(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 July 2004 (08.07.2004)

PCT

(10) International Publication Number
WO 2004/056368 A1

(51) International Patent Classification[7]: A61K 31/506, A61P 5/48, 9/00, 17/14, 25/00

(21) International Application Number: PCT/GB2003/005558

(22) International Filing Date: 18 December 2003 (18.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0229581.4 19 December 2002 (19.12.2002) GB

(71) Applicant *(for all designated States except US)*: **CYCLACEL LIMITED** [GB/GB]; 12 St James's Square, London SW1Y 4RB (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WANG, Shudong** [AU/GB]; Burnside Mill, Forfar, Angus DD8 2RZ (GB). **MEADES, Christopher** [GB/GB]; 32 Chirnside Place, Whitehazel Park, Dundee DD4 0TE (GB). **WOOD, Gavin** [GB/GB]; Whinrig, Millbank, Cupar, Fife KY15 5DP (GB). **DUNCAN, Kenneth** [GB/GB]; 73 Woolcarders Court, Hayford Mill, Cambusbarron, Stirlingshire FK7 9RA (GB). **ZHEVELA, Daniella** [GB/GB]; 28 West Acres Drive, Newport on Tay, Fife DD6 8NR (GB). **FISCHER, Peter** [GB/GB]; Denley Lodge, 1 Arbirlot Road, Arbroath, Angus DD11 2EN (GB).

(74) Agents: **CLYDE-WATSON, Zoe** et al.; D Young & Co., 21 New Fetter Lane, London EC4A 1DA (GB).

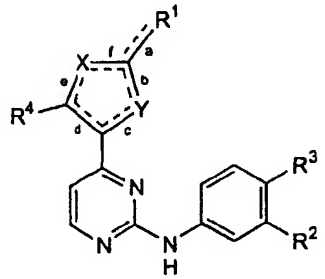
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

[Continued on next page]

(54) Title: THERAPEUTIC APPLICATIONS OF 2-SUBSTITUTED 4-HETEROARYLRYRIMIDINES



(I)

(57) **Abstract:** The present invention relates to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein (A) one of X and Y is S, and the other is N; or one of X and Y is NH or N-R^5, and the other is C-R^6; "a" is a single bond; "b", "c", "d", "e" and "f' are single or double bonds so as to form a heteroaryl ring; R^1 is is R^7 with the proviso that R^1 is other than H or Me; or (B) one of X and Y is S, and the other is NH or N-R^5; "a" and "d" are each double bonds; "b", "c", "e" and "f' are each single bonds; R^1 is oxo; and R^2, R^3, R^4, R^5, and R^6 are each independently H or R^7; R^7 is a group $(CH_2)_n$-R^8, wherein n is 0, 1, 2, 3 or 4 and wherein $R^8$is selected from alkyl, aryl, heteroaryl, heterocycloalkyl, F, Cl, Br, I, CF_3, NO_2, CN, OH, O-alkyl, O-aryl, 0- heteroaryl, 0-heterocycloalkyl, CO-alkyl, CO-aryl, CO-heteroaryl, CO-heterocycloalkyl, COO-alkyl, NH_2, NH-alkyl, NH-aryl, N(alkyl)$_2$, NH-heteroaryl, NH-heterocycloalkyl, COOH, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$, CONH-aryl, CONH-heteroaryl, CONHheterocycloalkyl, SO_3H, $S0_2$-alkyl, SO_2-aryl, $S0_2$-heteroaryl, SO_2-heterocycloalkyl, SO_2NH_2, SO_2NH-alkyl, SO_2N(alkyl)$_2$, SO_2NH-aryl, SO_2NH-heteroaryl, or SO_2NHheterocycloalkyl, wherein said alkyl, aryl, heteroaryl, and heterocycloalkyl groups are optionally substituted with one or more groups selected from halogeno, NO_2, OH, 0methyl, NH_2, COOH, $CONH_2$ and CF_3; in the preparation of a medicament for treating diabetes. The compounds of the invention also have applications in the treatment of CNS disorders, alopecia, cardiovascular disorders and stroke.

WO 2004/056368 A1

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

THERAPEUTIC APPLICATIONS OF 2-SUBSTITUTED 4-HETEROARYLRYRIMIDINES

The present invention relates to new therapeutic applications of 2-substituted 4-heteroaryl-pyrimidines.

BACKGROUND TO INVENTION

Certain 4,5,6-substituted-N-(substituted-phenyl)-2-pyrimidineamines having anti-asthmatic properties are disclosed in EP-A-233,461. Certain 4-heteroaryl-N-(3-substituted-phenyl)-2-pyridineamines possessing anti-proliferative properties and inhibiting protein kinase C, epidermal growth factor receptor-associated tyrosine protein kinase (EGF-R-TPK), as well as CDK1/cyclin B have been disclosed in WO95/09847 wherein the exemplified heteroaryl groups are pyridyl and indolyl.

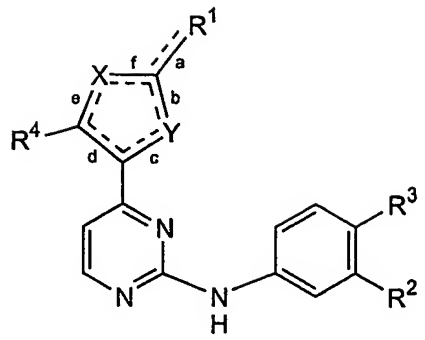
J. Med. Chem. (1993) Vol. 36, pages 2716-2725, Paul, R. et al discloses a further class of phenyl amino-pyrimidines possessing anti-inflammatory activity. These compounds include mono-substituted 2-thienyl groups at the 4-position of the pyrimidine ring and dimethyl-3-furyl groups at this position.

We have previously disclosed certain anti-proliferative thiazolo- and pyrrolo-anilinopyrimidines (WO 01/072745, Cyclacel Limited; WO 02/079193, Cyclacel Limited). The compounds disclosed therein were surprisingly found not to inhibit protein kinase C.

The present invention relates to previously undisclosed therapeutic applications of 2-substituted 4-heteroaryl-pyrimidines.

STATEMENT OF INVENTION

A first aspect of the invention relates to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof,



I

wherein

(A) one of X and Y is S, and the other is N; or

one of X and Y is NH or N-R^5, and the other is C-R^6;

"a" is a single bond;

"b", "c", "d", "e" and "f" are single or double bonds so as to form a heteroaryl ring;

R^1 is is R^7 with the proviso that R^1 is other than H or Me; or

(B) one of X and Y is S, and the other is NH or N-R^5;

"a" and "d" are each double bonds;

"b", "c", "e" and "f" are each single bonds;

R^1 is oxo; and

R^2, R^3, R^4, R^5, and R^6 are each independently H or R^7;

R^7 is a group $(CH_2)_n$-R^8, wherein n is 0, 1, 2, 3 or 4 and wherein R^8 is selected from alkyl, aryl, heteroaryl, heterocycloalkyl, F, Cl, Br, I, CF_3, NO_2, CN, OH, O-alkyl, O-aryl, O-heteroaryl, O-heterocycloalkyl, CO-alkyl, CO-aryl, CO-heteroaryl, CO-heterocycloalkyl, COO-alkyl, NH_2, NH-alkyl, NH-aryl, N(alkyl)$_2$, NH-heteroaryl, NH-heterocycloalkyl, COOH, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$, CONH-aryl, CONH-heteroaryl, CONH-heterocycloalkyl, SO_3H, SO_2-alkyl, SO_2-aryl, SO_2-heteroaryl, SO_2-heterocycloalkyl, SO_2NH_2, SO_2NH-alkyl, SO_2N(alkyl)$_2$, SO_2NH-aryl, SO_2NH-heteroaryl, or SO_2NH-heterocycloalkyl, wherein said alkyl, aryl, heteroaryl, and heterocycloalkyl groups are

optionally substituted with one or more groups selected from halogeno, NO_2, OH, O-methyl, NH_2, COOH, $CONH_2$ and CF_3;
in the preparation of a medicament for treating diabetes.

A second aspect of the invention relates to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined above in the preparation of a medicament for treating a CNS disorder.

A third aspect of the invention relates to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined above in the preparation of a medicament for treating a cardiovascular disorder.

A fourth aspect of the invention relates to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined above in the preparation of a medicament for treating a stroke.

A fifth aspect of the invention relates to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined above in the preparation of a medicament for treating alopecia.

A sixth aspect of the invention relates to a method of treating a GSK3-dependent disorder, said method comprising administering to a subject in need thereof, a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined above in an amount sufficient to inhibit GSK3.

DETAILED DESCRIPTION

As used herein, the term "alkyl" includes both saturated straight chain and branched alkyl groups which may be substituted (mono- or poly-) or unsubstituted. Preferably, the alkyl group is a C_{1-20} alkyl group, more preferably a C_{1-15}, more preferably still a C_{1-12} alkyl

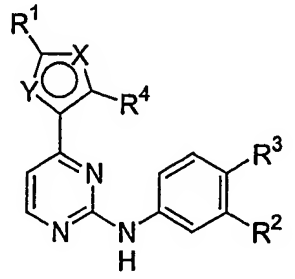
group, more preferably still, a C_{1-6} alkyl group, more preferably a C_{1-3} alkyl group. Particularly preferred alkyl groups include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl.

As used herein, the term "aryl" refers to a substituted (mono- or poly-) or unsubstituted monoaromatic or polyaromatic system, wherein said polyaromatic system may be fused or unfused. Preferably, the term "aryl" is includes groups having from 6 to 10 carbon atoms, e.g. phenyl, naphthyl etc. More preferably, the aryl group contains 6 carbons, for example, a phenyl group. The term "aryl" is synonymous with the term "aromatic".

As used herein, the term "heteroaryl" refers to five- and six-membered aromatic rings containing up to 4 heteroatoms, each independently selected from N, O, and S. Preferred heteroaryl groups include pyrrole, pyrazole, pyrimidine, pyrazine, pyridine, quinoline, thiazole, thiophene and furan.

As used herein, the term "heterocycloalkyl" refers to saturated or unsaturated five- and six-membered cyclic systems containing up to 4 heteroatoms each independently selected from N, O, and S.

In one preferred embodiment, the invention relates to the use of a compound of formula Ia, or a pharmaceutically acceptable salt thereof,



Ia

wherein

one of X and Y is N and the other is S; or

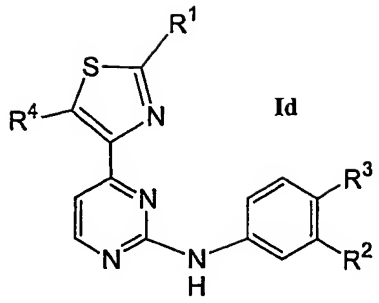
one of X and Y is NH or N-R^5 and the other is C-R^6;

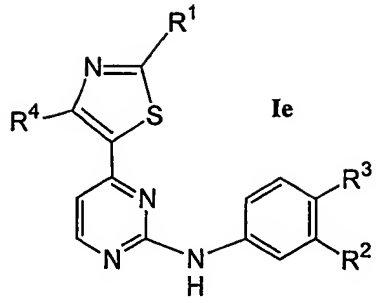
R^1 is R^7 with the proviso that R^1 is other than H or Me.

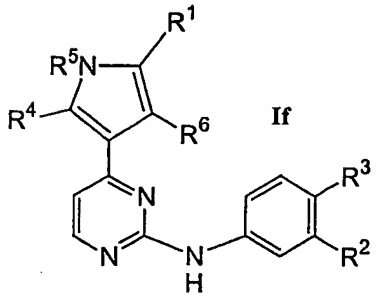
R^2, R^3, R^4, R^5, and R^6 are each independently H or R^7;

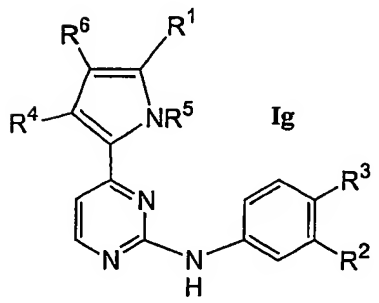
R^7 is a group $(CH_2)_n$-R^8, wherein n is 0, 1, 2, 3 or 4 and wherein R^8 is selected from alkyl, aryl, heteroaryl, heterocycloalkyl, F, Cl, Br, I, CF_3, NO_2, CN, OH, O-alkyl, O-aryl, O-heteroaryl, O-heterocycloalkyl, CO-alkyl, CO-aryl, CO-heteroaryl, CO-heterocycloalkyl, COO-alkyl, NH_2, NH-alkyl, NH-aryl, N(alkyl)$_2$, NH-heteroaryl, NH-heterocycloalkyl, COOH, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$, CONH-aryl, CONH-heteroaryl, CONH-heterocycloalkyl, SO_3H, SO_2-alkyl, SO_2-aryl, SO_2-heteroaryl, SO_2-heterocycloalkyl, SO_2NH_2, SO_2NH-alkyl, SO_2N(alkyl)$_2$, SO_2NH-aryl, SO_2NH-heteroaryl, or SO_2NH-heterocycloalkyl, wherein said alkyl, aryl, heteroaryl, and heterocycloalkyl groups are optionally substituted with one or more groups selected from halogeno, NO_2, OH, O-methyl, NH_2, COOH, $CONH_2$ and CF_3;
in the preparation of a medicament for treating diabetes.

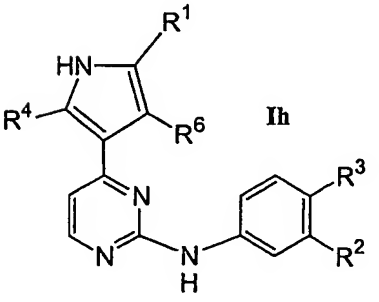
Preferred compounds of the invention include those of formula Id, Ie, If, Ig, Ih and Ii shown below.

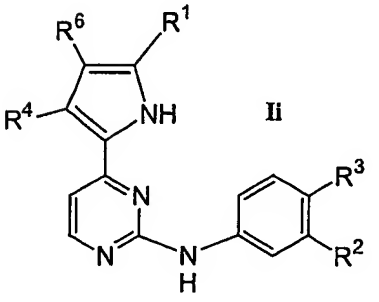












For compounds of formula Ia, in a first preferred embodiment, X is N and Y is S; or X is NH or N-R^5 and Y is C-R^6.

Preferably, for said first preferred embodiment:

R^1 is selected from CN, $CONH_2$, NO_2, halo, $CH_2N(alkyl)_2$, O-alkyl, NH_2 and NH-alkyl;

R^2 is selected from NO_2, H, OH, halo and alkyl;

R^3 is selected from H, halo, OH, CF_3, alkyl, $N(alkyl)_2$, O-alkyl, heterocycloalkyl and COO-alkyl;

R^4 is alkyl;

R^5 is H or alkyl; and

R^6 is alkyl.

Even more preferably, for said first preferred embodiment:

R^1 is selected from CN, $CONH_2$, NO_2, Br, Cl, CH_2NMe_2, OMe, NH_2 and NHMe;

R^2 is selected from NO_2, H, OH, I, Me, F and Cl;

R^3 is selected from H, F, OH, CF_3, I, Me, Cl, NMe_2, OMe, morpholino and COOEt;

R^4 is Me;

R^5 is H or Me; and

R^6 is Me.

For compounds of formula Ia, in a second preferred embodiment, X is NH or N-R^5 and Y is C-R^6.

Preferably, in said second preferred embodiment,

R^1 is selected from CN, $CONH_2$, NO_2, halo and $CH_2N(alkyl)_2$;

R^2 is selected from NO_2, H, OH, halo and alkyl;

R^3 is selected from H, halo, OH, CF_3, alkyl and $N(alkyl)_2$;

R^4 is alkyl;

R^5 is H or alkyl; and

R^6 is alkyl.

Even more preferably, in said second preferred embodiment,

R^1 is selected from CN, $CONH_2$, NO_2, Br, Cl and CH_2NMe_2;

R^2 is selected from NO_2, H, OH, I, Me and F;

R^3 is selected from H, F, OH, CF_3, I, Me, Cl and NMe_2;

R^4 is Me;

R^5 is H or Me; and

R^6 is Me.

More preferably still, in said second preferred embodiment,

R^1 is CN or $CONH_2$;

R^2 is NO_2 or H; and

R^3 is F or Me.

In a third preferred embodiment of the invention, X is N and Y is S.

For said third preferred embodiment, preferably,

R^1 is selected from halo, NH_2 and NH-alkyl;

R^2 is selected from NO_2, H, OH, halo and alkyl;

R^3 is selected from H, halo, OH, alkyl, $N(alkyl)_2$, O-alkyl, heterocycloalkyl and COO-alkyl.;

R^4 is alkyl.

More preferably, in said third preferred embodiment,

R^1 is selected from Cl, NH_2 and NHMe;

R^2 is selected from NO_2, H, OH, Me and Cl; and

R^3 is selected from H, F, OH, Me, Cl, NMe_2, OMe, morpholino and COOEt;

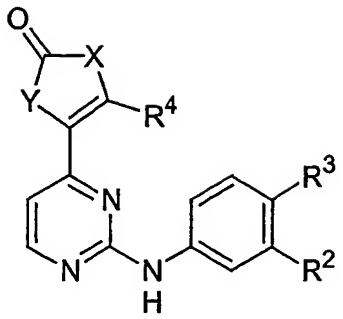
R^4 is Me.

More preferably still, in said third preferred embodiment,

R^2 is H or NO_2; and

R^3 is Cl or F.

Another alternative preferred embodiment of the invention relates to the use of a compound of formula Ib, or a pharmaceutically acceptable salt thereof,



Ib

wherein one of X and Y is S, and the other is NH or N-R^5; and

R^{2-5} are as defined above for formula I;

in the preparation of a medicament for treating diabetes.

In one particularly preferred embodiment, Y is S and X is NH or NR^5.

Preferably, for compounds of formula Ib:

R^2 is selected from H, OH, NO_2 and alkyl;

R^3 is selected from H, halogen, alkoxy, alkyl, N-$(alkyl)_2$ and OH; and

R^4 and R^5 are each independently alkyl.

More preferably, for compounds of formula Ib:

R^2 is selected from H, OH, NO_2 and Me;

R^3 is selected from H, Cl, F, OMe, Me, NMe_2 and OH; and

R^4 and R^5 are both Me.

In one especially preferred embodiment of the invention, the compound of formula I is selected from compounds [1]-[26] and [28]-[39] listed below.

Another aspect of the invention relates to the use of one or more of the following compounds in the preparation of a medicament for the treatment of a GSK-dependent disorder:

3,5-Dimethyl-4-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[1]**;

4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[2]**;

4-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[3]**;

3,5-Dimethyl-4-[2-(4-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[4]**;

4-[2-(4-Iodo-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[5]**;

4-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[6]**;

3,5-Dimethyl-4-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[7]**;

4-[2-(3-Iodo-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[8]**;

4-[2-(4-Chloro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[9]**;

4-[2-(3-Hydroxy-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[10]**;

4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[11]**;

4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[12]**;

4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide **[13]**;

[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[14]**;

N-[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-N',N'-dimethyl-benzene-1,4-diamine **[15]**;

[4-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[16]**;

[4-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine **[17]**;

[4-(5-Chloro-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[18]**;

[4-(5-Dimethylaminomethyl-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[19]**;

4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[20]**;

N^4-[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-N^1,N^1-dimethyl-2-nitro-benzene-1,4-diamine **[21]**;

4-[2-(3-Fluoro-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[22]**;

5-[2-(4-Chloro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[23]**;

5-[2-(4-Methoxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[24]**;

5-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[25]**;

5-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[26]**;

(4-Fluoro-phenyl)-[4-(2-methyl-4-phenyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-amine **[27]**;

5-[2-(4-Fluoro-3-nitro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[28]**;

2-Chloro-4-[4-(4-methyl-2-methylamino-thiazol-5-yl)-pyrimidin-2-ylamino]-benzoic acid ethyl ester **[29]**;

[4-(2-Amino-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine **[30]**;

3,4-Dimethyl-5-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[32]**;

5-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[33]**;

5-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[34]**;

[4-(2-Chloro-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine **[35]**;

3,4-Dimethyl-5-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[36]**;

5-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[37]**;

4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[38]**; and

4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[39]**.

More preferably, said compound of formula I is selected from the following:

3,5-Dimethyl-4-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[1]**;

4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[2]**;

4-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[6]**;

3,5-Dimethyl-4-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[7]**;

4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[11]**;

4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[12]**;

4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide **[13]**;

4-[2-(3-Fluoro-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[22]**;

(4-Fluoro-phenyl)-[4-(2-methyl-4-phenyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-amine **[27]**;

3,4-Dimethyl-5-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[32]**;

5-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[34]**;

3,4-Dimethyl-5-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[36]**;

5-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[37]**;

4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[38]**; and

4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[39]**.

Even more preferably, said compound of formula I is selected from the following:

3,5-Dimethyl-4-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[7]**;

4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide **[13]**;

(4-Fluoro-phenyl)-[4-(2-methyl-4-phenyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-amine **[27]**;

3,4-Dimethyl-5-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[32]**;

3,4-Dimethyl-5-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[36]**;

5-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[37]**;

4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[38]**; and

4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[39]**.

Most preferably, said compound of formula I is selected from the following:

4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[20]**; and

N^4-[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-N^1,N^1-dimethyl-2-nitro-benzene-1,4-diamine **[21]**.

In one particularly preferred embodiment of the invention, the compound of formula I is capable of inhibiting GSK3β. Preferably, said compound of formula I exhibits an IC_{50} value of less than 1 μM as measured by a GSK3β kinase assay. Details of a suitable GSK3β kinase assay are described in the accompanying Examples section. Preferably, said compound is selected from [1]-[3], [6], [7], [10], [11], [13]-[15], [17], [20]-[23] and

[25]-[29]. More preferably, said compound of formula I exhibits an IC_{50} value of less than 0.1 μM. More preferably, the compound is selected from [7], [13], [20], [21], [23], [25], [28], [32], [33], [34], [35], [36], [37] and [39]. Even more preferably, said compound of formula I exhibits an IC_{50} value less than 0.01 μM. Even more preferably, the compound is selected from [20], [28], [32] and [35]. More preferably still, said compound of formula I exhibits an IC_{50} value of less than 0.001 μM. More preferably still, the compound is selected from [32] and [35].

In another preferred embodiment, the compound of formula exhibits selectivity for inhibiting GSK3β over CDKs, for example CDK2/E, as measured by the appropriate kinase assays. Preferably, the compound exhibits a selectivity, IC_{50} (CDK2/E)/(GSK3β), of 2 or more. Preferably, the compound is selected from [7], [13], [20]-[23], [25]-[28], [32], [33] and [35]-[39]. More preferably, the compound exhibits a selectivity, IC_{50} (CDK2/E)/(GSK3β), of 5 or more. More preferably, the compound is selected from [7], [20], [23], [27], [28], [32], [33], [35], [38] and [39]. More preferably still, the compound exhibits a selectivity, IC_{50} (CDK2/E)/(GSK3β), of 10 or more. More preferably still, the compound is selected from [7], [20], [23], [27], [28], [32] and [35].

In another preferred embodiment, the compound of formula I is capable of inducing cellular glycogen synthase (GS) activity as measured by an appropriate assay. Preferably, the compound is selected from [1]-[3], [6], [7], [11]-[13], [20]-[22], [27], [32], [34] and [36]-[39]. More preferably, said compound exhibits a 3-fold or more increase in cellular GS activity over control samples. More preferably, the compound is selected from [1], [2], [6], [7], [21], [32], [36], [37] and [39].

THERAPEUTIC APPLICATIONS

As used herein the phrase "preparation of a medicament" includes the use of compounds of formula I directly as the medicament in addition to their use in a screening programme for

identifying further therapeutic agents or in any stage of the manufacture of such a medicament.

The compounds of formula I have therapeutic applications in the treatment of diabetes, CNS disorders (such as Alzheimer's disease and bipolar disorder), stroke, cardiovascular disorders, and alopecia.

Experiments undertaken by the applicant have demonstrated that compounds of formula I are capable of inhibiting glycogen synthase kinase 3 (GSK3). Glycogen synthase kinase 3 is a Ser/Thr protein kinase composed of two isoforms (α and β), which are highly homologous within the catalytic domain. For a recent review on GSK3 biology refer to Frame, S.; Cohen, P. *Biochem. J.*, 2001, **359**, 1.

It is known that some CDK inhibitors, including *e.g.* hymenialdisine (Meijer, L.; Thunnissen, A.-M.W.H.; White, A.W.; Garnier, M.; Nikolic, M.; Tsai, L.-H.; Walter, J.; Cleverley, K.E.; Salinas, P.C.; Wu, Y.-Z.; Biernat, J.; Mandelkow, E.M.; Kim, S.-H.; Pettit, G.R. *Chem. Biol.*, 2000, **7**, 51), paullones (Leost, M.; Schultz, C.; Link, A.; Wu, Y.-Z.; Biernat, J.; Mandelkow, E.-M.; Bibb, J.A.; Snyder, G.L.; Greengard, P.; Zaharevitz, D.W.; Gussio, R.; Senderowicz, A.M.; Sausville, E.A.; Kunick, C.; Meijer, L. *Eur. J. Biochem.*, 2000, **267**, 5983), and indirubins (Leclerc, S.; Garnier, M.; Hoessel, R.; Marko, D.; Bibb, J.A.; Snyder, G.L.; Greengard, P.; Biernat, J.; Wu, Y.-Z.; Mandelkow, E.-M.; Eisenbrand, G.; Meijer, L. J. *Biol. Chem.*, 2001, **276**, 251) also inhibit GSK3. On the other hand, other CDK inhibitor molecules that do not inhibit GSK3, *e.g.* roscovitine (Havlicek, L.; Hanus, J.; Vesely, J.; Leclerc, S.; Meijer, L.; Shaw, G.; Strnad, M. *J. Med. Chem.*, 1997, **40**, 408) and other purine-based inhibitors (Chang, Y.T.; Gray, N.S.; Rosania, G.R.; Sutherlin, D.P.; Kwon, S.; Norman, T.C.; Sarohia, R.; Leost, M.; Meijer, L.; Schultz, P.G. *Chem. Biol.*, 1999, **6**, 361).

One aspect of the invention relates to the use of compounds of formula I, or pharmaceutically accetable salts thereof, in the preparation of a medicament for treating diabetes.

In a particularly preferred embodiment, the diabetes is type II diabetes.

GSK3 is one of several protein kinases that phosphorylate glycogen synthase (GS). The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of GS. The action of GSK3 on GS thus results in GS deactivation and thus suppression of the conversion of glucose into glycogen in muscles.

Type II diabetes (non-insulin dependent diabetes mellitus) is a multi-factorial disease. Hyperglycaemia is due to insulin resistance in the liver, muscles, and other tissues, coupled with impaired secretion of insulin. Skeletal muscle is the main site for insulin-stimulated glucose uptake, there it is either removed from circulation or converted to glycogen. Muscle glycogen deposition is the main determinant in glucose homeostasis and type II diabetics have defective muscle glycogen storage. There is evidence that an increase in GSK3 activity is important in type II diabetes (Chen, Y.H.; Hansen, L.; Chen, M.X.; Bjorbaek, C.; Vestergaard, H.; Hansen, T.; Cohen, P.T.; Pedersen, O. *Diabetes*, 1994, **43**, 1234). Furthermore, it has been demonstrated that GSK3 is over-expressed in muscle cells of type II diabetics and that an inverse correlation exists between skeletal muscle GSK3 activity and insulin action (Nikoulina, S.E.; Ciaraldi, T.P.; Mudaliar, S.; Mohideen, P.; Carter, L.; Henry, R.R. *Diabetes*, 2000, **49**, 263).

GSK3 inhibition is therefore of therapeutic significance in the treatment of diabetes, particularly type II, and diabetic neuropathy.

A further aspect of the invention relates to a method of treating diabetes comprising inhibiting GSK3 by administering to a subject in need thereof, a therapeutically effective

amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, such that treatment of diabetes occurs.

A further aspect of the invention relates to a method of inhibiting GSK3 in a cell comprising contacting said cell with an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, such that GSK3 is inhibited in said cell.

It is notable that GSK3 is known to phosphorylate many substrates other than GS, and is thus involved in the regulation of multiple biochemical pathways. For example, GSK is highly expressed in the central and peripheral nervous systems.

Another aspect of the invention therefore relates to the use of compounds of formula I, or pharmaceutically acceptable salts thereof, in the preparation of a medicament for treating a CNS disorders, for example neurodegenerative disorders.

Preferably, the CNS disorder is Alzheimer's disease.

Tau is a GSK-3 substrate which has been implicated in the etiology of Alzheimer's disease. In healthy nerve cells, Tau co-assembles with tubulin into microtubules. However, in Alzheimer's disease, tau forms large tangles of filaments, which disrupt the microtubule structures in the nerve cell, thereby impairing the transport of nutrients as well as the transmission of neuronal messages.

Without wishing to be bound by theory, it is believed that GSK3 inhibitors may be able to prevent and/or reverse the abnormal hyperphosphorylation of the microtubule-associated protein tau that is an invariant feature of Alzheimer's disease and a number of other neurodegenerative diseases, such as progressive supranuclear palsy, corticobasal degeneration and Pick's disease. Mutations in the tau gene cause inherited forms of fronto-

temporal dementia, further underscoring the relevance of tau protein dysfunction for the neurodegenerative process (Goedert, M. *Curr. Opin. Gen. Dev.*, 2001, **11**, 343).

Another aspect of the invention relates to the use of compounds of formula I, or pharmaceutically acceptable salts thereof, in the preparation of a medicament for treating bipolar disorder.

Yet another aspect of the invention relates to the use of compounds of formula I, or pharmaceutically acceptable salts thereof, in the preparation of a medicament for treating a stroke.

Reducing neuronal apoptosis is an important therapeutic goal in the context of head trauma, stroke, epilepsy, and motor neuron disease (Mattson, M.P. *Nat. Rev. Mol. Cell. Biol.*, 2000, **1**, 120). Therefore, GSK3 as a pro-apoptotic factor in neuronal cells makes this protein kinase an attractive therapeutic target for the design of inhibitory drugs to treat these diseases.

Another aspect of the invention relates to the use of compounds of formula I, or pharmaceutically acceptable salts thereof, in the preparation of a medicament for treating a cardiovascular disorder.

In one preferred embodiment, the cardiovascular disorder is myocardial infarction.

Yet another aspect of the invention relates to the use of compounds of formula I, or pharmaceutically acceptable salts thereof, in the preparation of a medicament for treating alopecia.

Hair growth is controlled by the Wnt signalling pathway, in particular Wnt-3. In tissue-culture model systems of the skin, the expression of non-degradable mutants of β-catenin

leads to a dramatic increase in the population of putative stem cells, which have greater proliferative potential (Zhu, A.J.; Watt, F.M. *Development*, 1999, *126*, 2285). This population of stem cells expresses a higher level of non-cadherin-associated β-catenin (DasGupta, R.; Fuchs, E. *Development*, 1999, **126**, 4557), which may contribute to their high proliferative potential. Moreover, transgenic mice overexpressing a truncated β-catenin in the skin undergo *de novo* hair-follicle morphogenesis, which normally is only established during embryogenesis. The ectopic application of GSK3 inhibitors may therefore be therapeutically useful in the treatment of baldness and in restoring hair growth following chemotherapy-induced alopecia.

A further aspect of the invention relates to a method of treating a GSK3-dependent disorder, said method comprising administering to a subject in need thereof, a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined above in an amount sufficient to inhibit GSK3.

Preferably, the compound of formula I, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to inhibit GSK3β.

Preferably, the GSK3-dependent disorder is selected from diabetes, a CNS disorder (such as Alzheimer's disease or bipolar disorder), stroke, cardiovascular disorders, and alopecia.

SALTS/ESTERS

The compounds used in the present invention can be present as salts or esters, in particular pharmaceutically acceptable salts or esters.

Pharmaceutically acceptable salts of the compounds of the invention (first and seconds aspects) include suitable acid addition or base salts thereof. A review of suitable pharmaceutical salts may be found in Berge et al, J Pharm Sci, 66, 1-19 (1977). Salts are formed, for example with strong inorganic acids such as mineral acids, e.g. sulphuric acid,

phosphoric acid or hydrohalic acids; with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted (e.g., by halogen), such as acetic acid; with saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or tetraphthalic; with hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid; with aminoacids, for example aspartic or glutamic acid; with benzoic acid; or with organic sulfonic acids, such as (C_1-C_4)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted (for example, by a halogen) such as methane- or p-toluene sulfonic acid.

Esters are formed either using organic acids or alcohols/hydroxides, depending on the functional group being esterified. Organic acids include carboxylic acids, such as alkanecarboxylic acids of 1 to 12 carbon atoms which are unsubstituted or substituted (e.g., by halogen), such as acetic acid; with saturated or unsaturated dicarboxylic acid, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or tetraphthalic; with hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid; with aminoacids, for example aspartic or glutamic acid; with benzoic acid; or with organic sulfonic acids, such as (C_1-C_4)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted (for example, by a halogen) such as methane- or p-toluene sulfonic acid. Suitable hydroxides include inorganic hydroxides, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide. Alcohols include alkanealcohols of 1-12 carbon atoms which may be unsubstituted or substituted, e.g. by a halogen).

ENANTIOMERS AND TAUTOMERS

In all aspects of the present invention previously discussed, the invention includes, where appropriate the use of all enantiomers and tautomers of compounds of formula I. The man skilled in the art will recognise compounds that possess an optical properties (one or more

chiral carbon atoms) or tautomeric characteristics. The corresponding enantiomers and/or tautomers may be isolated/prepared by methods known in the art.

POLYMORPHS

The invention furthermore relates to the compounds of use in the present invention in their various crystalline forms, polymorphic forms and (an)hydrous forms. It is well established within the pharmaceutical industry that chemical compounds may be isolated in any of such forms by slightly varying the method of purification and or isolation form the solvents used in the synthetic preparation of such compounds.

PRODRUGS

The invention further includes the compounds of use in the present invention in prodrug form. Such prodrugs are generally compounds of formula I wherein one or more appropriate groups have been modified such that the modification may be reversed upon administration to a human or mammalian subject. Such reversion is usually performed by an enzyme naturally present in such subject, though it is possible for a second agent to be administered together with such a prodrug in order to perform the reversion in vivo. Examples of such modifications include ester (for example, any of those described above), wherein the reversion may be carried out be an esterase etc. Other such systems will be well known to those skilled in the art.

PHARMACEUTICAL COMPOSITIONS

The present invention also encompasses the use of pharmaceutical compositions comprising the compounds of the invention. In this regard, and in particular for human therapy, even though the compounds of the present invention (including their pharmaceutically acceptable salts, esters and pharmaceutically acceptable solvates) can be administered alone, they will generally be administered in admixture with a

pharmaceutical carrier, excipient or diluent selected with regard to the intended route of administration and standard pharmaceutical practice.

Thus, the present invention also relates to the use of pharmaceutical compositions comprising one or more compounds of formula I or pharmaceutically acceptable salts or esters thereof, together with at least one pharmaceutically acceptable excipient, diluent or carrier.

By way of example, in the pharmaceutical compositions of the present invention, the compounds of use in the invention may be admixed with any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilising agent(s). Examples of such suitable excipients for the various different forms of pharmaceutical compositions described herein may be found in the "Handbook of Pharmaceutical Excipients, 2nd Edition, (1994), Edited by A Wade and PJ Weller.

ADMINISTRATION

The pharmaceutical compositions of the present invention may be adapted for oral, rectal, vaginal, parenteral, intramuscular, intraperitoneal, intraarterial, intrathecal, intrabronchial, subcutaneous, intradermal, intravenous, nasal, buccal or sublingual routes of administration.

For oral administration, particular use is made of compressed tablets, pills, tablets, gellules, drops, and capsules. Preferably, these compositions contain from 1 to 250 mg and more preferably from 10-100 mg, of active ingredient per dose.

Other forms of administration comprise solutions or emulsions which may be injected intravenously, intraarterially, intrathecally, subcutaneously, intradermally, intraperitoneally or intramuscularly, and which are prepared from sterile or sterilisable solutions. The

pharmaceutical compositions of the present invention may also be in form of suppositories, pessaries, suspensions, emulsions, lotions, ointments, creams, gels, sprays, solutions or dusting powders.

An alternative means of transdermal administration is by use of a skin patch. For example, the active ingredient can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin. The active ingredient can also be incorporated, at a concentration of between 1 and 10% by weight, into an ointment consisting of a white wax or white soft paraffin base together with such stabilisers and preservatives as may be required.

Injectable forms may contain between 10 - 1000 mg, preferably between 10 - 250 mg, of active ingredient per dose.

Compositions may be formulated in unit dosage form, i.e., in the form of discrete portions containing a unit dose, or a multiple or sub-unit of a unit dose.

DOSAGES

A person of ordinary skill in the art can easily determine an appropriate dose of one of the instant compositions to administer to a subject without undue experimentation. Typically, a physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The dosages disclosed herein are exemplary of the average case. There can of course be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

In an exemplary embodiment, one or more doses of 10 to 150 mg/day will be administered to the patient for the treatment of a viral disorder.

Preferably, said compound of formula I is administered in an amount sufficient to inhibit GSK3.

Even more preferably, said compound of formula I is administered in an amount sufficient to inhibit GSK3β.

COMBINATIONS

In a particularly preferred embodiment, the one or more compounds of the invention are administered in combination with one or more other pharmacologically active agents. In such cases, the compounds of the invention may be administered consecutively, simultaneously or sequentially with the one or more other pharmacologically active agents.

It is known in the art that many drugs are more effective when used in combination. In particular, combination therapy is desirable in order to avoid an overlap of major toxicities, mechanism of action and resistance mechanism(s). Furthermore, it is also desirable to administer most drugs at their maximum tolerated doses with minimum time intervals between such doses. The major advantages of combining drugs are that it may promote additive or possible synergistic effects through biochemical interactions and also may decrease the emergence of drug resistance which would have been otherwise responsive to initial treatment with a single agent.

Beneficial combinations may be suggested by studying the pharmacological activity of the test compounds with agents known or suspected of being valuable in the treatment of a particular disorder. This procedure can also be used to determine the order of administration of the agents, i.e. before, simultaneously, or after delivery.

The present invention is now described by way of example, and with reference to the accompanying figures, wherein:

Figure 1 shows the activation of cellular glycogen synthase activity by example compounds [20] and [21] in HEK293 cells (top), 3T3 mouse adipocyte cells (middle) and L6 rat myocyte cells (bottom), as measured by the fractional reaction velocity of the enzyme (the ratio between the activity at 0.1 and 10 mM glucose–6 phosphate substrate concentrations).

Figure 2 shows blood glucose levels (mmol/L) against time (minutes) for compound [20] in ZDF rats.

EXAMPLES

Table 1 shows the structures and chemical names of the exemplified compounds.

Example 1

3,5-Dimethyl-1H-pyrrole-2-carbonitrile

Ethyl cyanoacetate (10 mL, 94 mmol) was diluted with AcOH (20 mL) and the solution was cooled to –10 °C (ice-MeOH bath). $NaNO_2$ (6.5 g, 94 mmol) was dissolved in H_2O (10 mL) and the solution was added dropwise over a period of 40 min, keeping the internal temperature < 0° C. After completion of the addition, the reaction mixture was stirred for 1 h with cooling. It was then warmed to room temperature and stirred for a further 3 h. The mixture was diluted with AcOH (50 mL) and H_2O (50 mL). Pentane-2,4-dione (10.6 mL, 103 mmol) was added and the mixture heated to ~ 75 °C. To this reaction mixture Zn powder (6.9 g, 105 mmol) was added in portions over a period of 30 min at such a rate as to maintain the internal temperature < 90 °C. The reaction mixture was then heated for a further 30 min before pouring into H_2O (1 L). From the reaction mixture title compound (3.67 g) was filtered as an off-white solid. The filtrate was extracted with EtOAc (3 × 500 mL). The combined organic extracts were washed (brine) and dried ($MgSO_4$). The solvent was evaporated to a brown oil, which was purified by chromatography (100 g SiO_2' eluted with 4:1 heptane / EtOAc) to afford a further crop (4.41 g) of this product as a pale yellow solid (total yield 72 %).

4-Acetyl-3,5-dimethyl-1H-pyrrole-2-carbonitrile

3,5-Dimethyl-1*H*-pyrrole-2-carbonitrile (1.2 g, 10 mmol) was dissolved in anhydrous 1,2-dichloroethane (15 mL) and $AlCl_3$ (2.93 g, 22 mmol) was added in portions. The reaction vessel was purged with N_2 and was cooled in an ice-water bath. AcCl (0.71 mL, 10 mmol) was added dropwise and the mixture was stirred for 1 h with cooling and for a further 3 h at room temperature. The reaction mixture was quenched by careful addition of 2 M aq HCl. The acidity of the mixture was adjusted to approximately pH 6 by addition of $NaHCO_3$. After separation of the organic phase, the aqueous phase was extracted with EtOAc (3 × 100mL). The combined organic phases were washed (H_2O, then brine), dried ($MgSO_4$), and filtered. The solvent was evaporated to afford the title compound (1.42 g, 88 %) as a pale tan solid. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 8.75 (br. s, 1H, NH).

4-(3-Dimethylamino-acryloyl)-3,5-dimethyl-1H-pyrrole-2-carbonitrile

4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile (1.38 g, 8.51 mmol) was suspended in 1,1-bis-dimethylamino-3,3-dimethyl-butan-2-one (1.3 mL) and heated at 75 °C for 42 h. The reaction mixture was evaporated to dryness and the residue was purified by SiO_2 chromatography (heptane / EtOAc) to afford the title compound (1.2 g, 65 %) as a pale tan solid. ^{1}H-NMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.32 (s, 6H, CH_3), 5.22 (d, 1H, J = 12.4 Hz, CH), 7.47 (d 1H, J = 12.4 Hz, CH), 11.96 (br. s, 1H, NH).

3,5-Dimethyl-4-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile [1]

To a mixture of 4-(3-dimethylamino-acryloyl)-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile (1.0 mmol, 0.22 g) and 3-nitrophenyl guanidine nitrate (1.5 mmol, 0.36 g) in 2-methoxyethanol (5 mL) was added K_2CO_3 (138 mg, 1.0 mmol). The reaction mixture was heated at 120 °C under N_2 for 18 h. The solvent was evaporated to dryness and the residue was purified by flash chromatography (1:2 EtOAc / heptane) to afford the title compound as a light-yellow solid. M.p. 258-259 °C. MS: $[M+H]^+$ = 336.1 ($C_{17}H_{14}N_6O_2$ requires 334.3). ^{1}H-NMR (CD_3OD) δ: 2.39 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.94 (d, 1H, J = 5.1 Hz, pyrimidinyl-H),

7.50 (t, 1H, J = 8.3 Hz, Ph-H), 7.81 (m, 1H, Ph-H), 7.94 (m, 1H, Ph-H), 8.45 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 8.94 (t, 1H, J = 2.2 Hz, Ph-H).

The following compounds were prepared in a manner analogous to that described above:

4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[2]**
MS: $[M+H]^+$ = 307.7 ($C_{17}H_{14}FN_5$ requires 307.3). ^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.84 (d, 1H, J = 5.0 Hz, pyrimidinyl -H), 7.00 (m, 2H, Ph-H), 7.73 (m, 2H, Ph-H), 8.40 (d, 1H, J=5.5Hz, pyrimidinyl -H), 9.46 (s, 1H, NH), 12.19 (br. s, 1H, NH).

4-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[3]**
M.p. 272-276 °C. MS: $[M+H]^+$ =305.8 ($C_{17}H_{15}N_5O$ requires 305.3).^{1}H-NMR (CD_3OD) δ: 2.33 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.74-6.56 (m, 3H, pyrimidinyl-H/Ph-H), 7.36 (d, 2H, J = 8.5 Hz, Ph-H), 8.25 (d, 1H, J = 5.4 Hz, pyrimidinyl-H).

3,5-Dimethyl-4-[2-(4-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[4]**
M.p. 195.6-198.9 °C. MS: $[M+H]^+$ = 357.7 ($C_{18}H_{14}F_3N_5$ requires 357.3). ^{1}H-NMR ($CDCl_3$) δ: 2.33 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 6.75 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.20 (br. s, 1H, NH), 7.50 (d, 2H, J = 8.8 Hz, Ph-H), 7.71 (d, 2H, J = 8.8 Hz, Ph-H), 8.39 (d, 1H, J = 5.1 Hz, pyrimidinyl), 8.40 (br. s, 1H, NH).

4-[2-(4-Iodo-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[5]**
M.p. 178.3-181.2 °C. MS: $[M+H]^+$ = 416.6 ($C_{18}H_{14}IN_5$ requires 415.2). ^{1}H-NMR ($CDCl_3$) δ: 2.39 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.76 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.10 (br. s, 1H, NH), 7.44 (d, 2H, J = 8.8 Hz, Ph-H), 7.61 (d, 2H, J = 8.8 Hz, Ph-H), 8.42 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 8.45 (br. s, 1H, NH).

4-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[6]**
M.p. 247-250 °C. MS: $[M+H]^+$ =305.8 ($C_{17}H_{15}N_5O$ requires 305.3). ^{1}H-NMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.33 (m, 1H, Ph-H), 6.82 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.01 (t, 1H, J = 8.1 Hz, Ph-H), 7.11 (m, 1H, Ph-H), 7.33 (t, 1H, J = 2.1 Hz, Ph-H), 8.40 (d, 1H, J = 5.4 Hz, pyrimidinyl-H), 9.18 (s, 1H), 9.30 (s, 1H), 12.20 (br. s, 1H, NH).

3,5-Dimethyl-4-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[7]**
M.p. 233-237 °C. MS: $[M+H]^+$ = 350.0 ($C_{18}H_{16}N_6O_2$ requires 348.6). ^{1}H-NMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 6.92 (d, 1H, J = 5.4 Hz, pyrimidinyl-H), 7.39 (d, 1H, J = 8.5 Hz, Ph-H), 7.87 (dd, 1H, J = 8.1, 1.7 Hz, Ph-H), 8.48 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 8.63 (d, 1H, J = 1.7 Hz, Ph-H), 9.87 (s, 1H, NH), 12.21 (br. s, 1H, NH).

4-[2-(3-Iodo-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[8]**
M.p. 189.5-191.7 °C. MS: $[M+H]^+$ = 431.5 ($C_{18}H_{16}IN_5$ requires 429.6). ^{1}H-NMR (DMSO-d_6) δ: 2.29 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.85 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.20 (d, 1H, J = 8.1 Hz, Ph-H), 7.57 (m, 1H, Ph-H), 8.41-8.43 (m, 2H, Ph-H, pyrimidinyl-H), 9.48 (s, 1H, NH), 12.20 (br. s, 1H, NH).

4-[2-(4-Chloro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[9]**
M.p. 194.2-197.9 °C. MS: $[M+H]^+$ = 338.0 ($C_{18}H_{16}ClN_5$ requires 337.8). ^{1}H-NMR (DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.86 (d, 1H, J = 5.4 Hz, pyrimidinyl-H), 7.28 (d, 1H, J = 8.5 Hz, Ph-H), 7.61 (dd, 1H, J = 8.8, 2.4 Hz, Ph-H), 7.73 (d, 1H, J = 2.7 Hz, Ph-H), 8.43 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 9.51 (s, 1H, NH), 12.21 (br. s, 1H, NH).

4-[2-(3-Hydroxy-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile[10]

M.p. 221-225 °C. MS: $[M+H]^+ = 320.9$ ($C_{18}H_{17}N_5O$ requires 319.4). ^{1}H-NMR (DMSO-d_6) δ: 2.03 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.78 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 6.89 (d, 1H, J = 8.1 Hz, Ph-H), 7.02 (dd, 1H, J = 8.3, 1.7Hz, Ph-H), 7.29 (d, 1H, J = 0.7 Hz, Ph-H), 8.37 (d, 1H, J = 4.9 Hz, pyrimidinyl-H), 9.08 (s, 1H), 9.20 (s, 1H), 12.17 (br. s, 1H, NH).

4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile [11]

M.p. 161.3-164.1 °C. MS: $[M+H]^+ = 321.6$ ($C_{18}H_{16}FN_5$ requires 321.4). ^{1}H-NMR (DMSO-d_6) δ: 2.19 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.82 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.03 (t, 1H, J = 9.3 Hz, Ph-H), 7.53 (m, 1H, Ph-H), 7.61 (dd, 1H, J = 7.1, 2.4 Hz, Ph-H), 8.39 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 9.36 (s, 1H, NH), 12.20 (br. s, 1H, NH).

4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile [12]

M.p. 190.6-193.7 °C. MS: $[M+H]^+ = 334.7$ ($C_{19}H_{20}N_6$ requires 332.4). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.94 (br. s, 6H, CH_3), 6.66 (d, 1H, J = 5.6 Hz, pyrimidinyl-H), 6.79-6.80 (m, 2H, Ph-H), 7.05 (br. s, 1H, NH), 7.40-7.43 (m, 2H, Ph-H), 8.34 (d, 1H, J = 5.1Hz, pyrimidinyl-H), 8.52 (br. s, 1H, NH).

Example 2

4-(3-Dimethylamino-acryloyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide.

1-(2,4-Dimethyl-1*H*-pyrrol-3-yl)-ethanone (1.1 g, 10 mmol) was partially dissolved in a 2 M solution of NH_3 in MeOH and H_2O_2 (10 mL of a 27 % w/w solution in H_2O) was added dropwise over a period of 40 min at such a rate as to maintain the internal temperature ≤ 30 °C. The mixture was stirred for 18 h at room temperature. The resulting suspended white

solid was filtered and recrystallised from EtOAc to afford 4-acetyl-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide (1.06 g). An aliquot (720 mg, 4 mmol) was suspended in 1,1-bis-dimethylamino-3,3-dimethyl-butan-2-one (2 mL, 9.6mmol) in a N_2-flushed flask and heated at 75 °C for 48 h. The crude mixture was cooled and purified by SiO_2 chromatography (EtOAc / MeOH gradient elution). The title compound (449 mg) was obtained as a buff solid. ^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.90 (br. s, 2H, NH). 3.09 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 5.23 (d, 1H, J = 12.4 Hz, CH), 7.38 (d, 1H, J = 12.7 Hz, CH), 10.97 (br. s, 1H, NH).

4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide **[13]**

4-(3-Dimethylamino-acryloyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid amide (100 mg, 0.43 mmol), 4-fluorophenylguanidine nitrate (139 mg, 0.65 mmol) and K_2CO_3 (94 mg, 0.68 mmol) were partially dissolved in 2-methoxyethanol (5 mL) and heated at 120 °C for 18 h. The mixture was concentrated *in vacuo* and purified by SiO_2 chromatography (EtOAc / MeOH gradient elution). The crude product was triturated in iPr_2O to afford the title compound (31 mg) as a buff solid. M.p. 93.5-96.8 °C. MS: $[M+H^+]$ = 326.9 ($C_{17}H_{16}FN_5O$ requires 325.3). ^{1}H-NMR (DMSO-d_6) *δ*: 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.79 (d, 1H, *J* = 5.4 Hz, pyrimidinyl-H), 6.92 (br. s, 2H, NH), 7.07 (t, 2H, *J* = 8.5 Hz, Ph-H), 7.76-7.78 (m, 2H, Ph-H), 8.36 (d, 1H, *J* = 5.4 Hz, pyrimidinyl-H), 9.41 (s, 1H, NH), 11.24 (br. s, 1H, NH).

Example 3

3-Dimethylamino-1-(2,4-dimethyl-5-nitro-1H-pyrrol-3-yl)-propenone

HNO_3 (0.28 mL of a 69 % w/v aq solution, 4.37 mmol) was added dropwise to Ac_2O (5 mL) at room temperature, keeping the internal temperature ≤ 25 °C. The nitrating mixture was stirred at room temperature for 15 min before cooling to -40 °C. 1-(2,4-Dimethyl-1*H*-pyrrol-3-yl)-ethanone (500 mg, 3.64 mmol) was dissolved in Ac_2O (6 mL) and added dropwise, keeping the internal temperature ≤ -30 °C. The mixture was stirred at -40 °C for

30 min then at -10 °C for a further 30 min. The mixture was poured into ice-water (50 mL) and was extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed (brine), dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give a dark brown solid. This was recrystallised from MeOH to afford 1-(2,4-dimethyl-5-nitro-1*H*-pyrrol-3-yl)-ethanone (158 mg). An aliquot (150 mg, 0.82 mmol) was suspended in 1,1-bis-dimethylamino-3,3-dimethyl-butan-2-one (0.42 mL, 2.02 mmol) in a N_2-flushed flask and was heated at 70 °C for 18 h. The mixture was triturated in EtOAc to afford the title compound (119 mg) as a brown solid. ^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.80 (br. s, 3H, CH_3), 3.07 (br. s, 3H, CH_3), 5.19 (d, 1H, J = 12.7 Hz, CH), 7.45 (d, 1H, J = 12.4 Hz, CH), 12.76 (br, 1H, NH).

[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[14]**

3-Dimethylamino-1-(2,4-dimethyl-5-nitro-1*H*-pyrrol-3-yl)-propenone (110 mg, 0.46 mmol), 4-fluorophenyl guanidine nitrate (150 mg, 0.7 mmol), and K_2CO_3 (193 mg, 1.4 mmol) were partially dissolved in 2-methoxyethanol and heated at 120 °C for 18 h. The mixture was concentrated *in vacuo* and purified by SiO_2 chromatography (heptane / EtOAc gradient elution). The crude product was triturated in iPr_2O to afford the title compound (22 mg) as a pale orange solid. M.p. 166.3-170.1 °C. MS: $[M+H]^+$ = 329.3 ($C_{16}H_{14}FN_5O_2$ requires 327.3). ^{1}H-NMR (DMSO-d_6) δ: 2.49 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 6.73 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.04 (t, 2H, J = 8.8 Hz, Ph-H), 7.07 (br. s, 1H, NH), 7.55-7.58 (m, 2H, Ph-H), 8.44 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 9.40 (br. s, 1H, NH).

The following compound was prepared in analogous manner:

N-*[4-(2,4-Dimethyl-5-nitro-1*H*-pyrrol-3-yl)-pyrimidin-2-yl]*-N',N'-*dimethyl-benzene-1,4-diamine* **[15]**

M.p. 265-268 °C. MS: $[M+H]^+$ = 353.0 ($C_{18}H_{20}N_6O_2$ requires 352.4). ^{1}H-NMR (DMSO-d_6) δ: 2.39 (s, 3H, CH_3), 2.48 (br. s, 6H, CH_3), 2.82 (s, 3H, CH_3), 6.69 (d, 2H, J = 9.0 Hz, Ph-

H), 6.74 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.50 (d, 2H, J = 9.0 Hz, Ph-H), 8.38 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 9.18 (s, 1H, NH), 13.00 (br. s, 1H, NH).

Example 4

[4-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[16]**

[4-(2,4-Dimethyl-1*H*-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine (80 mg, 0.28 mmol) was dissolved in THF (4 mL) and cooled to –50 °C. *N*-Bromosuccinimide (55 mg, 0.31 mmol) was dissolved in THF (2 mL) and added dropwise, keeping the internal temperature ≤ -40 °C. The mixture was stirred for 1h with cooling then evaporated *in vacuo*. The residue was treated with H_2O (10 mL) and extracted with EtOAc (3 × 10mL). The combined organic extracts were washed (brine), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was purified by SiO_2 chromatography heptane / EtOAc gradient elution) to afford the title compound (19 mg) as an orange solid after recrystallisation from iPr_2O. M.p. 181.4-183.3 °C. MS: $[M+H]^+$ = 362.9 ($C_{16}H_{14}BrFN_4$ requires 361.2).^{1}H-NMR ($CDCl_3$) δ: 2.10 (s, 3H, CH_3), 2.36 (s, 3H, CH_3) 6.56 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 6.97 (t, 2H, J = 8.3Hz, Ph-H), 7.00 (br. s, 1H, NH), 7.79-7.52 (m, 2H, Ph-H), 8.85 (br. s, 1H, NH), 8.26 (d, 1H, J = 5.1 Hz, pyrimidinyl-H).

The following compound was prepared in analogous manner:

[4-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine **[17]**

M.p. 198.1-203 °C. MS: $[M+H]^+$ =389.3 ($C_{16}H_{14}BrN_5O_4$ requires 361.2). ^{1}H-NMR ($CDCl_3$) δ: 2.49 (s, 3H, CH_3), 2.59 (s, 3H, CH_3) 6.73 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.04 (t, 2H, J = 8.8 Hz, Ph-H), 7.57 (m, 2H, Ph-H), 7.90 (br. s, 1H, NH), 8.44 (d, 1H, J = 5.1Hz, pyrimidinyl-H), 9.40 (br. s, 1H, NH).

Example 5

[4-(5-Chloro-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[18]**

[4-(2,4-Dimethyl-1*H*-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine (80 mg, 0.28 mmol) was dissolved in THF (4 mL) and cooled to –60 °C. *N*-Chlorosuccinimide (41 mg, 0.31 mmol) was dissolved in THF (2 mL) and added dropwise, keeping the internal temperature ≤ -50 °C. The mixture was stirred for 30min with cooling then evaporated *in vacuo*. The residue was treated with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed (brine), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was purified by SiO_2 chromatography (heptane / EtOAc gradient elution) to afford the title compound (37 mg) as an orange solid after recrystallisation from iPr_2O. M.p. 200-203 °C. MS: $[M+H]^+ = 317.7$ ($C_{16}H_{14}ClFN_4$ requires 316.8). ^{1}H-NMR ($CDCl_3$) δ: 2.17 (s, 3H, CH_3), 2.42 (s, 3H, CH_3) 6.77 (d, 1H, $J = 5.9$ Hz, pyrimidinyl-H), 7.02-7.06 (m, 3H, Ph-h, NH), 7.54-7.56 (m, 2H, Ph-H), 7.95 (br. s, 1H, NH), 8.25 (d, 1H, $J = 5.4$ Hz, pyrimidinyl-H).

Example 6

[4-(5-Dimethylaminomethyl-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[19]**

Dimethylamine (40 µL, 0.31 mmol) was diluted with methanol (0.5 mL) and formaldehyde (30 µL of a 37 % w/w aq solution , 0.37 mmol) was added. [4-(2,4-Dimethyl-1*H*-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine (87 mg, 0.31 mmol) was added in small portions and the mixture was heated to reflux. After 1.5 h the mixture was diluted with H_2O (10 mL). The resulting precipitate was filtered and triturated in 2 M aq HCl. The mixture was filtered and the filtrate was washed with 2 M aq NaOH. The filtrate was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed (brine), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was purified by SiO_2 chromatography (heptane / EtOAc gradient elution) to afford the title compound (36 mg) as an orange solid after recrystallisation from iPr_2O. M.p. 88.4-91.6 °C. MS: $[M+H]^+ = 340.6$ ($C_{19}H_{22}FN_5$ requires 339.4).^{1}H-NMR ($CDCl_3$) δ: 2.18 (s, 3H, CH_3), 2.56 (s, 6H,

CH_3), 2.42 (s, 3H, CH_3), 3.38 (s, 2H, CH_2), 6.75 (d, 1H, J = 5.4 Hz, pyrimidinyl-H), 7.00 (t, 2H, J = 8.6 Hz, Ph-H), 7.13 (br. s, 1H, NH), 7.56-7.59 (m, 2H, Ph-H), 8.31 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 8.55 (br. s, 1H, NH).

Example 7

*4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile* **[20]**

This was obtained by reaction of 4-(3-dimethylamino-acryloyl)-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile and *N*-(4-dimethylamino-3-nitro-phenyl)-guanidine nitrate. The crude product was recrystallised from PhMe (21 %) as a yellow solid. ^{1}H NMR (CD_3OD) δ: 2.38 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.86 (s, 6H, CH_3), 6.76 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.02 (s, 1H, Ph-H), 7.04 (m, 1H, Ph-H), 7.49 (m, 1H, Ph-H), 8.29 (d, 1H, J = 2.7Hz, Ph-H), 8.40 (d, 1H, J = 5.4 Hz, pyrimidinyl-H), 8.94 (t, 1H, J = 2.2 Hz, Ph-H). MS *m/z* 378.71 $(M+H)^+$ ($C_{19}H_{19}N_7O_2$ requires 377.40).

Example 8

N^4-*[4-(2,4-Dimethyl-5-nitro-1*H*-pyrrol-3-yl)-pyrimidin-2-yl]*-N^1,N^1-*dimethyl-2-nitro-benzene-1,4-diamine* **[21]**

This was prepared by reaction of 3-dimethylamino-1-(2,4-dimethyl-5-nitro-1*H*-pyrrol-3-yl)-propenone and *N*-(4-dimethylamino-3-nitro-phenyl)-guanidine nitrate. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.87 (s, 6H, CH_3), 6.76 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.05 (m, 2H, Ph-H & NH), 7.48 (m, 1H, Ph-H), 8.32 (br. s, 1H, Ph-H), 8.44 (d, 1H, J = 5.1 Hz, pyrimidinyl-H).

Example 9

4-[2-(3-Fluoro-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[22]**

This compounds was prepared according to the general methods described in Example 1. M.p. 177.7-179.9 °C. MS: $[M+H]^+$ = 322.5 ($C_{18}H_{16}FN_5$ requires 321.3). ^{1}H-NMR (DMSO-

d_6) δ: 2.15 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.86 (d, 1H, J = 5.1 Hz, pyrimidinyl-H), 7.13 (t, 1H, J = 9.0 Hz, Ph-H), 7.36 (dd, 1H, J = 8.1, 1.7 Hz, Ph-H), 7.75 (dd, 1H, J = 12.9, 1.5 Hz, Ph-H), 8.43 (d, 1H, J = 5.4Hz, pyrimidinyl-H), 9.56 (s, 1H, NH), 12.21 (br. s, 1H, NH).

Example 10

*5-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3*H*-thiazol-2-one* **[34]**

To an ice-cooled solution of potassium thiocyanate (5.67 g, 58 mmol) in Me_2CO (45 mL) was added 3-chloro-pentane-2,4-dione (6.95 mL, 58 mmol) dropwise. After completion of the addition the reaction mixture was warmed to room temperature and stirred for a further 6 h. The solvent was evaporated to dryness. The residue was dissolved in EtOH (30 mL) and HCl (conc. aq, 15 mL) was added. The mixture was heated to reflux for 14 h. It was concentrated and the precipitate was collected, washed with cold MeOH and then Et_2O to afford 9.1 g of a pale solid. This compound was treated with *N,N*-dimethylformamide dimethylacetal (13 mL) at 100 – 110 °C for 8 h. The reaction mixture was concentrated and the residue was purified by SiO_2 flash chromatography (EtOAc/PE) to afford 5-(3-dimethylamino-acryloyl)-3,4-dimethyl-3*H*-thiazol-2-one. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (s, 3H, CH_3), 3.07 (s, 3H, CH_3), 3.21 (s, 6H, CH_3), 5.09 (d, 1H, J = 12.0 Hz, CH), 7.59 (d, 1H, J = 12.0 Hz, CH).

A solution of 5-(3-dimethylamino-acryloyl)-3,4-dimethyl-3*H*-thiazol-2-one (0.23 g, 1.0 mmol) in 2-methoxylethanol (3 mL) was treated with *N*-(4-hydroxy-phenyl)-guanidine nitrate (0.42 g, 2.0 mmol). After refluxing for 20 h the reaction mixture was concentrated and purified by SiO_2 flash chromatography (EtOAc). Recrystallisation from EtOAc afforded the tilted compound (25 mg) as brown crystals. Anal. RP-HPLC: t_R = 11.8 min (0 – 60 % MeCN in 0.1 % aq CF_3COOH over 20 min, 1 mL/min, purity > 95%). ^{1}H-NMR (DMSO-d_6) δ: 2.52 (s, 3H, CH_3), 3.27 (s, 3H, CH_3), 6.68 (d, 2H, J = 8.9 Hz, Ph-H), 6.81 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 7.44 (d, 2H, J = 8.9 Hz, Ph-H), 8.34 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 9.12 (br. s, 1H, OH/NH), 9.24 (br. s, 1H, NH/OH).

The following compounds were prepared in a similar manner to the procedures described above:

5-[2-(4-Chloro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[23]**

Light yellow solid; ^{1}H-NMR (DMSO-d_6) δ: 2.55 (s, 3H, CH_3), 3.29 (s, 3H, CH_3), 6.97 (d, 1H, J = 5.0 Hz, pyrimidinyl-H), 7.32 (d, 2H, J = 8.5 Hz, Ph-H), 7.76 (d, 2H, J = 9.0 Hz, Ph-H), 8.44 (d, 1H, J = 5.0 Hz, pyrimidinyl-H), 9.75 (br. s, 1H, NH).

5-[2-(4-Methoxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[24]**

Light yellow solid; ^{1}H-NMR (DMSO-d_6) δ: 2.54 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 6.86 (m, 3H, pyrimidinyl-H & Ph-H), 7.59 (d, 2H, J = 9.0 Hz, Ph-H), 8.37 (d, 1H, J = 5.0 Hz, pyrimidinyl-H), 9.39 (br. s, 1H, NH).

5-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[25]**

Light yellow solid; anal. RP-HPLC: t_R = 15.4 min (0 – 60 % MeCN in 0.1 % aq VF_3COOH over 20 min, 1 mL/min, purity > 95 %). ^{1}H-NMR (DMSO-d_6) δ: 2.55 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 6.36 (m, 1H, Ph-H), 6.90 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 7.03 (t, 1H, J = 8.5 Hz, Ph-H), 7.16 (m, 1H, Ph-H), 7.22 (s, 1H, Ph-H), 8.40 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 9.39 (br. s, 1H, NH).

5-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[26]**

Yellow solid; anal. RP-HPLC: t_R = 19.6 min (0 – 60 % MeCN in 0.1 % aq CF_3COOH over 20 min, 1 mL/min, purity > 95 %). ^{1}H-NMR (DMSO-d_6) δ: 2.83 (s, 3H, CH_3), 2.90 (s, 6H, CH_3), 3.08 (s, 3H, CH_3), 6.73 (m, 2H, Ph-H), 6.81(d, 1H, J = 5.5 Hz, pyrimidinyl-H), 7.03 (m, 1H, Ph-H), 7.50 (m, 1H, Ph-H), 8.32 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 9.24 (br. s, 1H, NH).

5-[2-(4-Fluoro-3-nitro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[28]**
Brown solid; ^{1}H-NMR (DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 6.36 (m, 1H, Ph-H), 6.91 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 7.31 (m, 1H, Ph-H), 8.33 (m, 1H, Ph-H), 8.48 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 8.52 & 9.68 (br. s, 1H, NH).

3,4-Dimethyl-5-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[32]**
Brown crystals. Anal. RP-HPLC: t_R = 17.8 min (0 – 60 % MeCN in 0.1 % aq CF_3COOH over 20 min, 1 mL/min, purity > 97%). ^{1}H-NMR (DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 6.92 (d, 1H, J = 5.0 Hz, pyrimidinyl-H), 7.42 (d, 1H, J = 8.0 Hz, Ph-H) 7.65 (m, 1H, Ph-H), 7.88 (m, 1H, Ph-H), 8.37 (d, 1H, J = 5.0Hz, pyrimidinyl-H), 8.72 (br. s, 1H, NH).

5-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[33]**
Gray solid; ^{1}H-NMR (DMSO-d_6) δ: 2.92 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 7.32 (d, 1H, J = 5.0 Hz, pyrimidinyl-H), 7.51 (m, 2H, Ph-H), 8.11 (m, 2H, Ph-H), 8.80 (d, 1H, J = 5.0 Hz, pyrimidinyl-H).

3,4-Dimethyl-5-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[36]**
Yellow solid; ^{1}H-NMR (DMSO-d_6) δ: 2.44 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.27 (s, 3H, CH_3), 7.03 (d, 1H, J = 5.0 Hz, pyrimidinyl-H), 7.40 (t, 1H, J = 8.5 Hz, Ph-H), 7.84 (m, 1H, Ph-H), 8.48 (d, 1H, J = 5.0 Hz, pyrimidinyl-H), 8.59 (s, 1H, Ph-H), 9.99 (br. s, 1H, NH).

5-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[37]**
Grey solid; ^{1}H-NMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 6.92 (d, 1H, J = 5.0 Hz, pyrimidinyl-H), 7.04 (t, 1H, J = 9.0 Hz, Ph-H), 7.48 (m, 1H, Ph-H), 7.68 (m, 1H, Ph-H), 8.40 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 9.54 (br. s, 1H, NH).

Example 11

2-Chloro-4-guanidino-benzoic acid ethyl ester

A solution of 2-chloro-4-phenylguanidino-benzoic acid (1.17g, 4.0 mmol) in absolute EtOH (4 mL) was treated with conc. H_2SO_4 (1 mL). After refluxing for 2 h the reaction mixture was cooled and poured into ice water (5 mL). This solution was treated with ammonia solution (1 mL). The resulting precipitates were collected and washed with Et_2O to afford the title compound as an off-white solid. ^{1}H-NMR (DMSO-d_6) δ: 1.31 (t, 3H, J = 7.1 Hz, CH_3), 4.31 (m, 2H, CH_2), 7.29 (m, 1H, Ph-H), 7.43 (s, 1H, Ph-H), 7.68 (br. s, 2H, NH_2) and 7.85 (m, 1H, Ph-H).

2-Chloro-4-[4-(4-methyl-2-methylamino-thiazol-5-yl)-pyrimidin-2-ylamino]-benzoic acid ethyl ester **[29]**

A mixture of 2-chloro-4-guanidino-benzoic acid ethyl ester (0.76 g, 3.0 mmol) and 3-Dimethylamino-1-(4-methyl-2-methylamino-thiazol-5-yl)-propenone (0.43 g, 2.0 mmol) in 2-methoxylethanol (5 mL) was treated with NaOH (80 mg). After refluxing for 24 h the reaction mixture was concentrated. The resulting precipitates were collected and recrystallised from MeOH to afford the title compound (149 mg) as a gray solid. ^{1}H-NMR (DMSO-d_6) δ: 1.35 (t, 3H, J = 7.1 Hz, CH_3), 4.36 (m, 2H, CH_2), 6.94 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 7.41-7.51 (m, 2H, Ph-H), 7.90 (s, 1H, Ph-H), 9.36 (d, 1H, J = 5.5 Hz, pyrimidinyl-H) and 9.56 (br. s, 1H, NH).

Example 12

1-(2-Amino-4-methyl-thiazol-5-yl)-ethanone

A mixture of thiourea (5.18 g, 0.068 mol) in dry MeOH (20 mL) was stirred and cooled on an ice bath. Pyridine (2 mL) was added, followed by 3-chloro-2,4-pentadione (9.15 g, 0.068 mol) dropwise. After completion of the addition the reaction mixture was allowed to warm to room temperature and stirring was continued for 4 h. The precipitates were filtered and washed with EtOAc to afford the title compound as a white solid.

N'-*[5-(3-Dimethylamino-acryloyl)-4-methyl-thiazol-2-yl]*-N,N-*dimethyl-formamidine*

A solution of 1-(2-amino-4-methyl-thiazol-5-yl)-ethanone (3.35 g, 0.021 mol) in *N,N*-dimethylformamide dimethylacetal (10 mL) was refluxed under N_2 for 4 – 6 h. The reaction mixture was evaporated to dryness. EtOAc was added to the residue and the precipitates were collected by filtration and were washed with EtOAc/PE (5:1, v/v) to afford the title compound as an orange solid (50 – 79 %). ^{1}H-NMR ($CDCl_3$) δ: 2.64 (s, 3H, CH_3), 3.08 (s, 6H, CH_3), 3.11 (s, 6H, CH_3), 5.35 (d, 1H, J = 12.2 Hz, CH), 7.67 (d, 1H, J = 12.2 Hz, CH), 8.23 (s, 1H, N=CH). DE MALDI-TOF MS: $[M+H]^+$ = 267.49 ($C_{12}H_{18}N_6OS$ requires 266.36).

[4-(2-Amino-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine **[30]**

A mixture of *N'*-[5-(3-dimethylamino-acryloyl)-4-methyl-thiazol-2-yl]-*N,N*-dimethyl-formamidine (2.19 g, 8.2 mmol) and 3-nitrophenyl guanidine nitrate (2.00 g 8.2 mmol) in 2-methoxyethanol (10 mL) was treated with NaOH (0.33 g). After refluxing under N_2 for 20 h the reaction mixture was concentrated and purified by silica-gel chromatography using EtOAc/PE (7:1) to elute the title compound as a light-yellow solid (1.95 g, 72 %), which was then recrystallised from EtOAc/MeOH. ^{1}H-NMR (DMSO-d_6) δ: 3.13 (s, 3H, CH_3), 7.02 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 7.59 (m, 4H, Ph-H and NH_2), 7.82 (m, 1H, Ph-H), 8.16 (m, 1H, Ph-H), 8.44 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 8.86 (br. s, 1H, NH).

Example 13

[4-(2-Chloro-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine **[35]**

A solution of [4-(2-methoxy-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine (0.71 g, 2.0 mmol) in $CHCl_3$ (2 mL) and DMF (0.14 mL) was cooled on an ice bath and was treated with $SOCl_2$ (1.5 mL). The reaction mixture was warmed to room temperature and then heated at reflux for 1.5 h. The reaction mixture was concentrated, poured into ice water (3 mL), and extracted with CH_2Cl_2. The organic phase was washed with brine, dried on $MgSO_4$, and filtered. The solvent was evaporated and the residue was recrystallised from CH_2Cl_2 to afford the title compound (61 mg) as a light yellow solid.

Anal. RP-HPLC: t_R = 22.7 min (0 – 60 % MeCN in 0.1 % aq CF_3COOH over 20 min, 1 mL/min, purity > 95 %). ^{1}H-NMR (DMSO-d_6) δ: 3.56 (s, 3H, CH_3), 6.61 (d, 1H, J = 5.5 Hz, pyrimidinyl-H), 7.31 (t, 1H, J = 8.2 Hz, Ph-H), 7.54 (m, 1H, Ph-H), 7.81 (m, 1H, Ph-H) and 8.32 (m, 2H, pyrimidinyl-H and Ph-H).

Example 14

4-Acetyl-3,5-dimethyl-1H-pyrrole-2-carbonitrile

Chlorosulfonyl isocyanate (1.60 mL, 18.38 mmol) in acetonitrile (10 mL) was slowly added to a suspension of 1-(2,4-dimethyl-1*H*-pyrrol-3-yl)-ethanone (1.87 g, 13.63 mmol) in anhydrous acetonitrile (15 mL) and dimethylformamide (5.0 mL) at –5 °C. The reaction mixture was stirred for 2 h before allowing to warm to room temperature overnight. The reaction mixture was then extracted from ice/water (100 mL) into ethyl acetate (4 x 100 mL). The organics were combined, washed with brine, dried over anhydrous magnesium sulfate and concentrated to yield a light brown solid, which was re-crystallised from diethyl ether to afford the title compound (1.52 g, 72 %). ^{1}H-NMR (d_6-DMSO) δ: 2.29 (3H, s, CH_3), 2.34 (3H, s, CH_3), 2.41 (3H, s, $COCH_3$), 12.34 (1H, s, NH).

4-Acetyl-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile

A solution of 4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile (0.567 g, 3.5 mmol) in tetrahydrofuran (5 mL) was added to a cooled (0 °C) slurry of sodium hydride (0.168 g, 7.0 mmol) in tetrahydrofuran (5mL). The reaction mixture was heated to 40 °C and methyl iodide (350 μL, 5.25 mmol) was added and the reaction mixture stirred for 2 h. After cooling, the reaction was quenched with saturated aqueous sodium carbonate solution (50 mL) and extracted into ethyl acetate (3 x 50 mL) before drying over anhydrous magnesium sulfate to afford the title compound as a yellow oil (0.443 g, 72 %) after removal of solvent. ^{1}H-NMR (d_6-DMSO) δ: 2.32 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.45 (3H, s, $COCH_3$), 3.58 (3H, s, NCH_3).

4-(3-Dimethylamino-acryloyl)-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile

4-Acetyl-1,3,5-trimethyl-1*H*-pyrrole-2-carbonitrile (0.352 g, 2 mmol) was taken up in *tert*-butoxybis(dimethylamino)methane (496 μL, 2.40 mmol) and heated at 75 °C for 22 h. The reaction mixture was dissolved in methanol (10 mL) and concentrated to yield a dark coloured oil. After addition of diethyl ether (20 mL), the dark brown solid product (0.442 g, 95 %) was filtered off to afford the title compound. ^{1}H NMR (d_6-DMSO) δ: 2.20 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.80 & 3.07 (6H, s, $N(CH_3)_2$), 3.54 (3H, s, NCH_3), 5.17 (1H, d, C=CH, J = 12.5 Hz), 7.45 (1H, d, C=CH, J = 12.5 Hz) .

4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[38]**

4-(3-Dimethylamino-acryloyl)-1,3,5-trimethyl-1*H*-pyrrole-2-carbonitrile (0.115 g, 0.5 mmol), *N*-(4-dimethylamino-phenyl)-guanidine nitrate (0.120 g, 0.5 mmol), and potassium carbonate (0.139 g, 1.0 mmol) were combined in 2-methoxyethanol (4 mL) and the mixture was heated at 115 °C for 22 h. After cooling, the inorganics were filtered off and the filtrate was concentrated to dryness. The crude product was purified by silica gel column chromatography to afford the title compound (53 mg, 31 %). ^{1}H-NMR (d_6-DMSO) δ: 2.27 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.83 (6H, s, $N(CH_3)_2$), 3.63 (3H, s, NCH_3), 6.68 (2H, d, ArH, J = 8.8 Hz), 6.71 (1H, d, ArH, J = 5.4 Hz), 7.51 (2H, d, ArH, J = 8.8 Hz), 8.35 (1H, d, ArH, J = 5.4 Hz), 9.11 (1H, s, NH). ESI-MS: m/z 347 (M^+ + 1).

4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[39]**

4-(3-Dimethylamino-acryloyl)-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile (0.115 g, 0.5 mmol), *N*-(4-dimethylamino-3-nitro-phenyl)-guanidine nitrate (0.143 g, 0.5 mmol), and potassium carbonate (0.139 g, 1.0 mmol) were combined in 2-methoxyethanol (4 mL) and the mixture was heated at 115 °C for 22 h. After cooling, the inorganics were filtered off and the filtrate was concentrated to dryness. The crude product was purified by silica gel column column to afford the title compound (76 mg, 39 %). ^{1}H-NMR (d_6-DMSO) δ: 2.29

(3H, s, CH_3), 2.43 (3H, s, CH_3), 2.74 (6H, s, $N(CH_3)_2$), 3.64 (3H, s, NCH_3), 6.84 (1H, d, ArH, J = 4.9 Hz), 7.23 (1H, d, ArH, J = 8.8 Hz), 7.78 (1H, dd, ArH, J = 8.8, 2.9 Hz), 8.38 (1H, d, ArH, J = 2.9 Hz), 8.45 (1H, d, ArH, J = 4.9 Hz), 9.66 (1H, s, NH). ESI-MS: m/z 392 (M^+ + 1).

Example 15

GSK-3β kinase assay

GSK-3 was obtained from New England Biolabs (UK) Ltd., Hitchin, Herts. The recombinant enzyme was isolated from a strain of *E. coli* that carries a clone expressing GSK-3β derived from a rabbit skeletal muscle cDNA library [Wang, Q.M.; Fiol, C.J.; DePaoli-Roach, A.A.; Roach, P.J. *J. Biol. Chem.*, 1994, **269**, 14566]. Inhibition of GSK-3 function was assessed by measurement of phosphorylation of CREB phosphopeptide KRREILSRRPphosphoSYR in the presence of test compounds. Using a 96-well assay format, GSK3 (7.5U) was incubated for 30 min at 30 °C in a total volume of 25 μL in 20 mM MOPS pH 7.2, 25 mM β-glycerophosphate, 5 mM EGTA, 1 mM DTT, 1 mM Na_3VO_3, 40 μM CREB peptide, 15 mM $MgCl_2$ and 100 μM ATP (containing 0.25 μCi [γ-^{32}P]-ATP) in the presence of varying concentrations of test compound. The samples were transferred to 96-well p81 filter plates (Whatman Polyfiltronics, Kent, UK), and the plates were washed 4 times with 200 μL/well of 75 mM aq orthophosphoric acid. Scintillation liquid (50 μL) was added to each well, and incorporated radioactivity for each sample was determined using a scintillation counter (TopCount, Packard Instruments, Pangbourne, Berks, UK).

CDK/cyclin kinase assays

Compounds were investigated for their CDK2/cyclin E, CDK2/cyclin A, CDK1/cyclin B, and CDK4/cyclin D1 inhibitory activity. His_6-tagged recombinant human cyclin-dependent kinases CDK1/cyclin B1, CDK2/cyclin E, CDK2/cyclin A, and CDK4 were expressed in sf9 insect cells using a baculovirus expression system. Recombinant cyclin D1 was expressed in *E. coli*. Proteins were purified by metal chelate affinity chromatography to

greater than 90 % homogeneity. Kinase assays were performed in 96-well plates using recombinant CDK/cyclins. Assays were performed in assay buffer (25 mM β-glycerophosphate, 20 mM MOPS, 5 mM EGTA, 1 mM DTT, 1 mM Na_3VO_3, pH 7.4), into which were added 2 - 4 μg of active enzyme with appropriate substrates (purified histone H1 for CDK1 and CDK2, recombinant GST-retinoblastoma protein (residues 773-928) for CDK4). The reaction was initiated by addition of Mg/ATP mix (15 mM $MgCl_2$ + 100 μM ATP with 30-50 kBq per well of [γ-^{32}P]-ATP) and mixtures incubated for 10 – 45 min, as required, at 30 °C. Reactions were stopped on ice, followed by filtration through p81 or GF/C filterplates (for CDK4) (Whatman Polyfiltronics, Kent, UK). After washing 3 times with 75 mM aq orthophosphoric acid, plates were dried, scintillant added and incorporated radioactivity measured in a scintillation counter (TopCount, Packard Instruments, Pangbourne, Berks, UK). Compounds for kinase assays were made up as 10 mM stocks in DMSO and diluted into 10 % DMSO in assay buffer. Data was analysed using curve-fitting software (GraphPad Prism version 3.00 for Windows, GraphPad Software, San Diego California USA) to determine IC_{50} values (concentration of test compound which inhibits kinase activity by 50 %.).

Example 16

Differentiation of L6 rat myocytes and 3T3 mouse adipocytes

Rat skeletal muscle myoblasts L6/G8.C5 were seeded at 2.4 x 10^5 cells per 10 cm dish in DMEM 10 % foetal calf serum (FCS), containing penicillin/streptomycin. When 90 % confluence was reached the medium was exchanged with α MEM, supplemented with 2 % FCS and penicillin/streptomycin. Medium was refreshed every 48 hours and 4-7 days later the myocytes were formed.

Mouse pre-adipocytes 3T3-F442A were seeded at 9 x 10^5 cells per 10 cm dish in DMEM 10 % FCS, containing penicillin/streptomycin. When 90 % confluent, the same medium was supplemented with 1 μg/mL insulin. After 3-5 days (when most cells were differentiated) insulin was removed and 4 days later the cells were ready to use.

Glycogen synthase (GS) assay

Cells on 10 cm dishes (Human Embryonic Kidney (HEK) 293 cells, L6 rat myocytes, or 3T3 mouse adipocytes) were treated with different concentrations of GSK3-inhibitors or DMSO vehicle for 90 min. Incubation medium was removed and cells were washed with ice-cold phosphate-buffered saline (PBS) prior to lysis on ice in 50 mM HEPES, pH 7.5, 10 mM EDTA, 100 mM NaF, 5 mM DTT, protease inhibitor cocktail (Sigma). After a freeze/thaw cycle the samples are sonicated for 10 sec and centrifuged at 15,000 g for 10 min at 4 °C. Lysate supernatants were snap-frozen on liquid nitrogen and stored at –80 °C. Lysates were assayed for glycogen synthase activity in buffer (50 mM Tris-HCl, pH 7.8, 20 mM EDTA, 25 mM NaF, 5 mM DTT, 1% glycogen, 0.3 mM UDP-glucose and 0.06 μCi of [^{14}C]-UDP-glucose in the presence of 0.1 or 10 mM glucose-6-phosphate. The reaction was carried out for 30 min at 30 °C. 70 μL of the reaction mixture (total volume 90 μL) were transferred to a GFC 96-well filter plate (bottom sealed with foil), containing 140 μL 96 % ethanol. The GFC plate was incubated for 1 h on ice and than washed with 66 % ethanol. To each well 100 μL scintillant liquid was added and the radioactivity of the samples was measured using a scintillation counter (Topcount, HP). Data are expressed as -fold increase in glycogen synthase activity ratios over those of control samples.

The biological activity of the exemplified compounds are summarised in Table 2. Activation of cellular glycogen synthase activity by example compounds [20] and [21] is shown in Figure 1.

Compounds [20] and [21] increased the activity of glycogen synthase in HEK293, rat myocyte, and mouse adipocyte cells, measured by the fractional reaction velocity of the enzyme (the ratio between the activity at 0.1 and 10 mM glucose–6 phosphate substrate concentrations). Both compounds increased the activity of GS in a dose-dependent manner. At 1 μM both compounds induced 2- and 4-fold activation of GS in myocytes and adipocytes, respectively.

Example 18

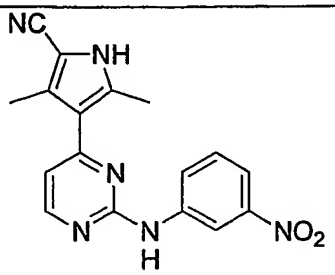
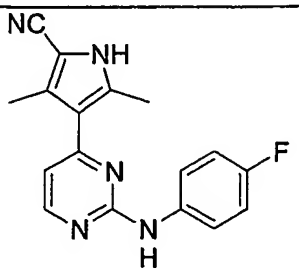
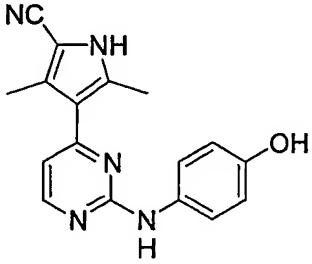
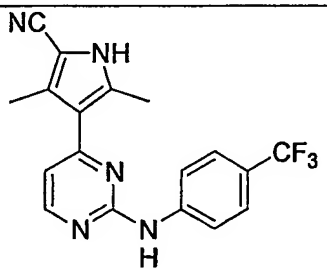
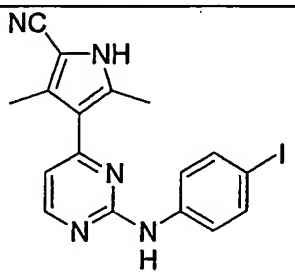
Oral glucose tolerance test (OGTT)

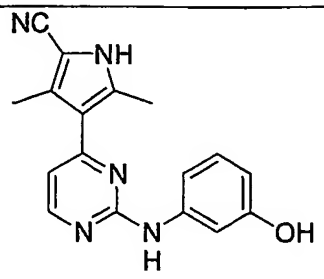
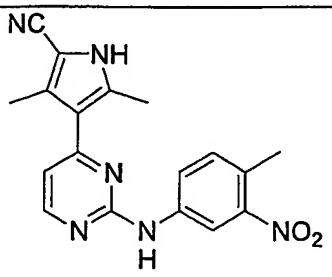
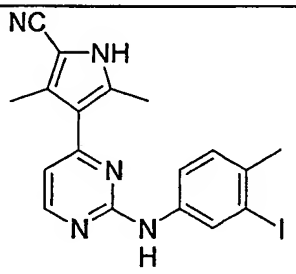
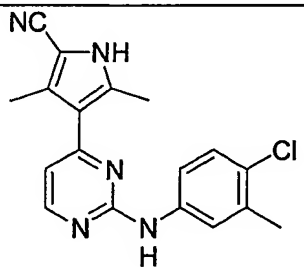
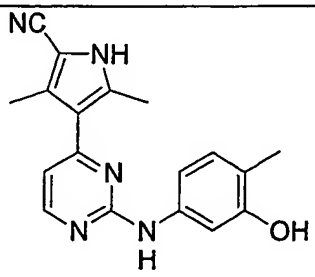
For the OGTT male ZDF fa/fa rats (Charles River, USA), 10-11 weeks old, were used. After 15 h fasting the animals were dosed intravenously with 5 mg/kg test compound in dosing vehicle, or with dosing vehicle (10 % DMSO, 90 % PEG-400) only at –270 and –30 min. At 0 min the rats were given 2 g/kg glucose by oral gavage. Plasma samples were taken before and every 15 min after the OGTT for determination of blood glucose. The results are shown in Figure 2.

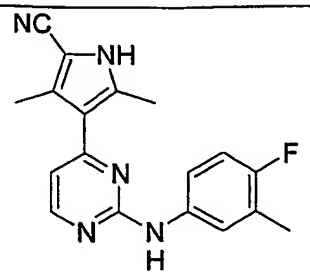
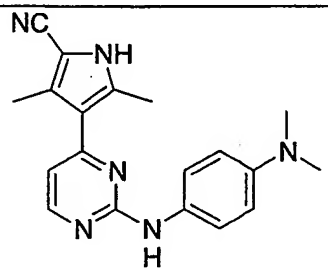
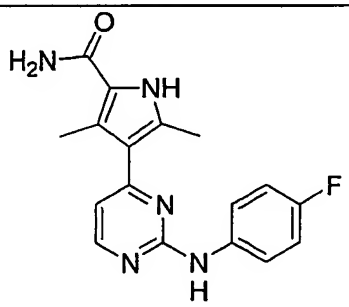
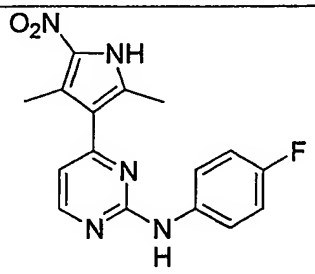
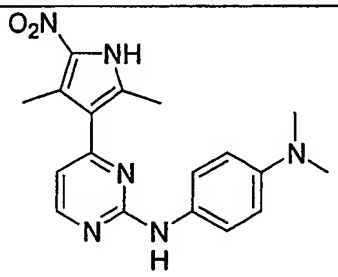
Compound [20] improved the glucose tolerance in ZDF rats significantly. Compound [20] decreased the reactive and absolute AUC by 39 and 22 %, respectively. Insulin levels also decreased after treatment with compound [20], suggesting that the glucose lowering effect is due to the improvement of the insulin resistance rather than increase of the insulin level. This confirms the proposed mechanism of action for GSK3 inhibitors.

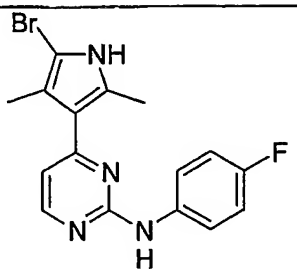
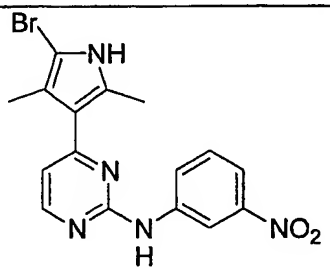
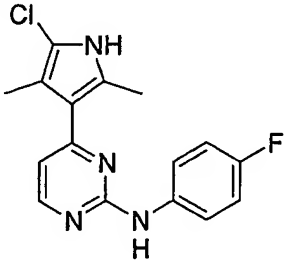
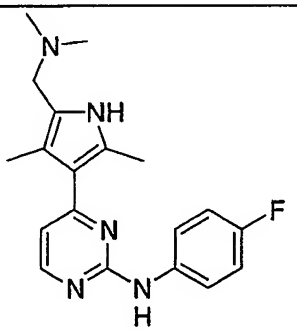
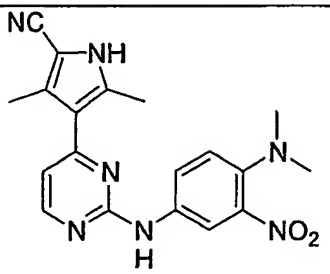
Various modifications and variations of the described methods of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, various modifications of the described modes for carrying out the invention which are obvious to those skilled in chemistry or related fields are intended to be within the scope of the following claims.

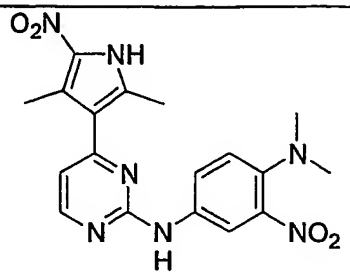
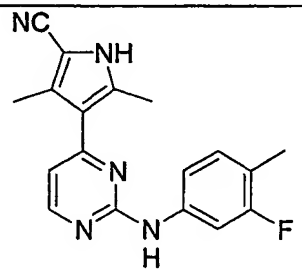
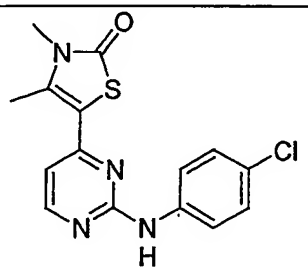
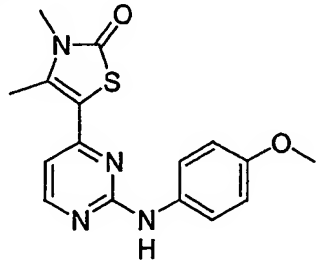
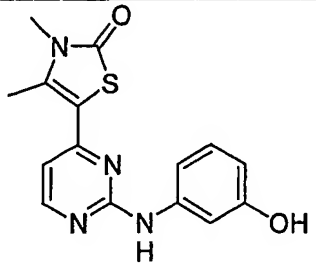
Table 1: Exemplified compounds

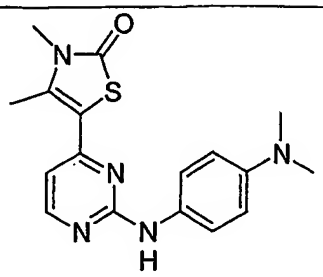
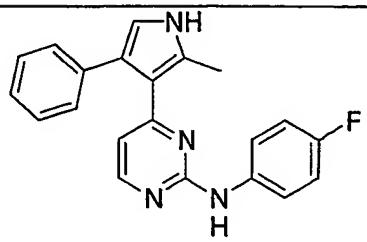
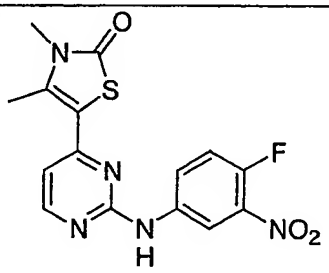
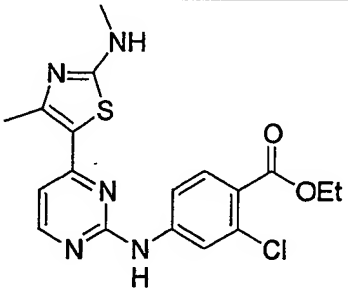
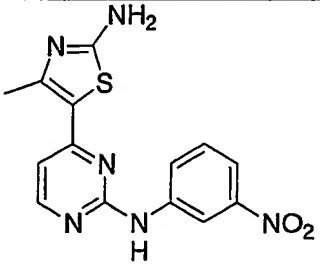
Number	Structure	Name
1		3,5-Dimethyl-4-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile
2		4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile
3		4-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile
4		3,5-Dimethyl-4-[2-(4-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile
5		4-[2-(4-Iodo-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile

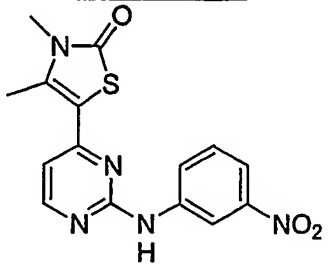
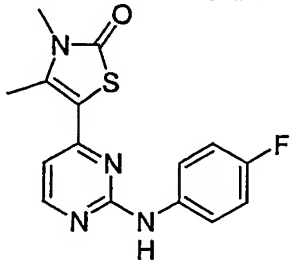
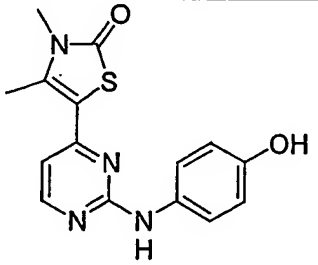
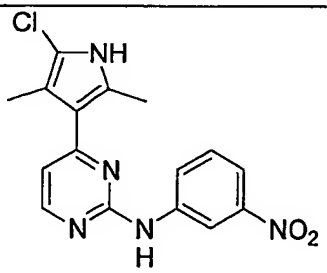
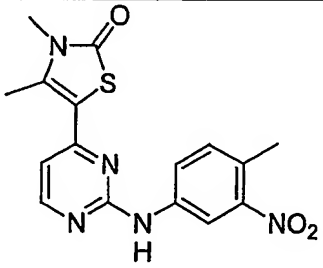
6		4-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile
7		3,5-Dimethyl-4-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile
8		4-[2-(3-Iodo-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile
9		4-[2-(4-Chloro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile
10		4-[2-(3-Hydroxy-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile

11		4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile
12		4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile
13		4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide
14		[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine
15		N-[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-N',N'-dimethyl-benzene-1,4-diamine

16		[4-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine
17		[4-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine
18		[4-(5-Chloro-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine
19		[4-(5-Dimethylaminomethyl-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine
20		4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile

21		N^4-[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-N^1,N^1-dimethyl-2-nitro-benzene-1,4-diamine
22		4-[2-(3-Fluoro-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile
23		5-[2-(4-Chloro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one
24		5-[2-(4-Methoxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one
25		5-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one

26		5-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one
27		(4-Fluoro-phenyl)-[4-(2-methyl-4-phenyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-amine
28		5-[2-(4-Fluoro-3-nitro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one
29		2-Chloro-4-[4-(4-methyl-2-methylamino-thiazol-5-yl)-pyrimidin-2-ylamino]-benzoic acid ethyl ester
30		[4-(2-Amino-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine

32		3,4-Dimethyl-5-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one
33		5-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one
34		5-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one
35		[4-(5-Chloro-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine
36		3,4-Dimethyl-5-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one

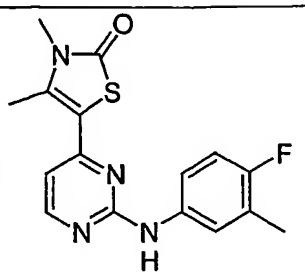
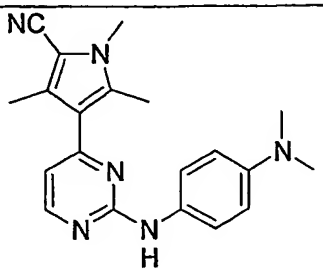
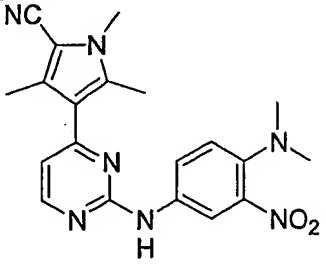
37		5-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one
38		4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile
39		4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile

Table 2: Biological activity of exemplified compounds

Compound No.	Kinase inhibition IC_{50} (μM)					Selectivity[a]	-Fold induction of GS activity[b]
	GSK3β	CDK2/E	CDK2/A	CDK1/B1	CDK4/D1		
1	0.21	0.03	n/d	n/d	0.25	0.1	3.0
2	0.15	0.09	n/d	n/d	0.39	0.6	4.0
3	0.19	0.09	n/d	n/d	0.14	0.4	1.6
4	2.4	0.18	n/d	n/d	2.5	0.1	n/d
5	1.5	0.55	n/d	n/d	1.1	0.4	n/d
6	0.16	0.04	n/d	n/d	0.10	0.2	3.9
7	0.04	0.39	n/d	n/d	0.58	11	3.0
8	1.8	0.86	n/d	n/d	0.98	0.5	n/d
9	3.4	1.0	n/d	n/d	4.0	0.3	n/d
10	0.28	0.15	n/d	n/d	0.32	0.5	n/d
11	0.29	0.05	n/d	n/d	0.36	0.2	2.8
12	1.2	0.54	n/d	n/d	0.37	0.5	1.2
13	0.05	0.22	n/d	n/d	0.19	4	2.3
14	0.80	0.06	n/d	n/d	0.22	0.1	n/d
15	0.95	0.96	n/d	n/d	1.0	1.0	n/d
16	3.2	0.55	n/d	n/d	3.0	0.2	n/d
17	0.28	0.37	n/d	n/d	4.0	1.3	n/d
18	2.5	0.73	n/d	n/d	3.6	0.3	n/d
19	14	0.14	n/d	n/d	4.5	0.01	n/d
20	0.005	0.15	0.10	0.05	0.16	30	2.4
21	0.04	0.14	0.25	0.30	1.02	3.5	3.3
22	0.34	0.76	n/d	n/d	2.07	2.2	2.8
23	0.03	0.29	0.74	1.96	2.9	10	n/d
24	1.1	0.76	0.70	0.97	1.1	0.7	n/d
25	0.04	0.09	0.09	0.51	1.1	2.3	n/d
26	0.64	1.5	0.75	2.47	0.95	2.4	n/d
27	0.50	> 50	n/d	n/d	n/d	>100	1.8
28	0.002	0.17	0.08	1.03	1.8	85	n/d
29	0.37	0.10	n/d	n/d	n/d	0.3	n/d
30	0.22	0.0002	n/d	n/d	0.41	0.001	n/d
32	0.0007	0.06	n/d	n/d	0.23	86	5.4
33	0.02	0.12	n/d	n/d	1.12	6.7	n/d
34	0.09	0.05	n/d	n/d	0.60	0.5	1.8

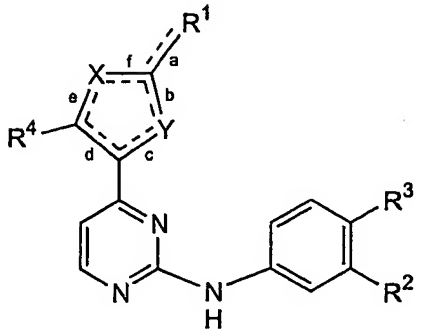
35	0.0007	0.01	n/d	n/d	0.58	13	n/d
36	0.03	0.11	n/d	0.20	n/d	4.5	3.0
37	0.05	0.13	n/d	1.10	n/d	2.7	3.5
38	0.12	1.1	0.93	2.8	1.3	9.2	1.3
39	0.019	0.16	0.22	0.18	1.4	8.4	3.0

[a] IC_{50} (CDK2/E) / IC_{50} (GSK3β)

[b] In HEK293 cells at [compound] = 5 μM

CLAIMS

1. Use of a compound of formula I, or a pharmaceutically acceptable salt thereof,



I

wherein

(A) one of X and Y is S, and the other is N; or

one of X and Y is NH or N-R^5, and the other is C-R^6;

"a" is a single bond;

"b", "c", "d", "e" and "f" are single or double bonds so as to form a heteroaryl ring;

R^1 is is R^7 with the proviso that R^1 is other than H or Me; or

(B) one of X and Y is S, and the other is NH or N-R^5;

"a" and "d" are each double bonds;

"b", "c", "e" and "f" are each single bonds;

R^1 is oxo; and

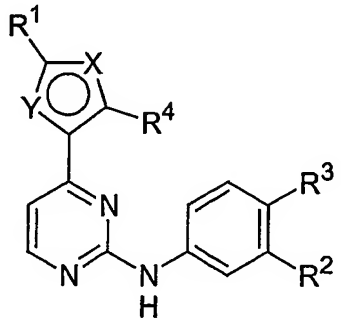
R^2, R^3, R^4, R^5, and R^6 are each independently H or R^7;

R^7 is a group $(CH_2)_n$-R^8, wherein n is 0, 1, 2, 3 or 4 and wherein R^8 is selected from alkyl, aryl, heteroaryl, heterocycloalkyl, F, Cl, Br, I, CF_3, NO_2, CN, OH, O-alkyl, O-aryl, O-heteroaryl, O-heterocycloalkyl, CO-alkyl, CO-aryl, CO-heteroaryl, CO-heterocycloalkyl, COO-alkyl, NH_2, NH-alkyl, NH-aryl, N(alkyl)$_2$, NH-heteroaryl, NH-heterocycloalkyl, COOH, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$, CONH-aryl, CONH-heteroaryl, CONH-

heterocycloalkyl, SO_3H, SO_2-alkyl, SO_2-aryl, SO_2-heteroaryl, SO_2-heterocycloalkyl, SO_2NH_2, SO_2NH-alkyl, $SO_2N(alkyl)_2$, SO_2NH-aryl, SO_2NH-heteroaryl, or SO_2NH-heterocycloalkyl, wherein said alkyl, aryl, heteroaryl, and heterocycloalkyl groups are optionally substituted with one or more groups selected from halogeno, NO_2, OH, O-methyl, NH_2, COOH, $CONH_2$ and CF_3;

in the preparation of a medicament for treating diabetes.

2. Use according to claim 1 wherein said compound is of formula Ia,



Ia

wherein

one of X and Y is N and the other is S; or

one of X and Y is NH or N-R^5 and the other is C-R^6;

R^1 is R^7 with the proviso that R^1 is other than H or Me.

R^{1-7} are as defined in claim 1.

3. Use according to claim 2 wherein X is N and Y is S; or X is NH or N-R^5 and Y is C-R^6.

4. Use according to claim 2 or claim 3 wherein:
R^1 is selected from CN, $CONH_2$, NO_2, halo, $CH_2N(alkyl)_2$, O-alkyl, NH_2 and NH-alkyl;
R^2 is selected from NO_2, H, OH, halo and alkyl;
R^3 is selected from H, halo, OH, CF_3, alkyl, $N(alkyl)_2$, O-alkyl, heterocycloalkyl and COO-alkyl;
R^4 is alkyl;
R^5 is H or alkyl; and
R^6 is alkyl.

5. Use according to any one of claims 2 to 4 wherein:
R^1 is selected from CN, $CONH_2$, NO_2, Br, Cl, OMe, CH_2NMe_2, NH_2 and NHMe;
R^2 is selected from NO_2, H, OH, I, Me, F and Cl;
R^3 is selected from H, F, OH, CF_3, I, Me, Cl, NMe_2, OMe, morpholino and COOEt;
R^4 is Me;
R^5 is H or Me; and
R^6 is Me.

6. Use according to any one of claims 2 to 5 wherein X is NH or N-R^5 and Y is C-R^6.

7. Use according to claim 6 wherein:
R^1 is selected from CN, $CONH_2$, NO_2, halo and $CH_2N(alkyl)_2$;
R^2 is selected from NO_2, H, OH, halo and alkyl;
R^3 is selected from H, halo, OH, CF_3, alkyl and $N(alkyl)_2$;
R^4 is alkyl;
R^5 is H or alkyl; and
R^6 is alkyl.

8. Use according to claim 7 wherein:
R^1 is selected from CN, $CONH_2$, NO_2, Br, Cl and CH_2NMe_2;
R^2 is selected from NO_2, H, OH, I, Me and F;
R^3 is selected from H, F, OH, CF_3, I, Me, Cl and NMe_2;
R^4 is Me;
R^5 is H or Me; and
R^6 is Me.

9. Use according to claim 8 wherein:
R^1 is CN or $CONH_2$;
R^2 is NO_2 or H; and
R^3 is F or Me.

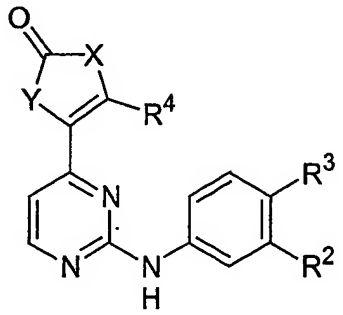
10. Use according to any one of claims 2 to 5 wherein X is N and Y is S.

11. Use according to claim 10 wherein:
R^1 is selected from halo, NH_2 and NH-alkyl;
R^2 is selected from NO_2, H, OH, halo and alkyl;
R^3 is selected from H, halo, OH, alkyl, $N(alkyl)_2$, O-alkyl, heterocycloalkyl and COO-alkyl; and
R^4 is alkyl.

12. Use according to 11 wherein:
R^1 is selected from Cl, NH_2 and NHMe;
R^2 is selected from NO_2, H, OH, Me and Cl; and
R^3 is selected from H, F, OH, Me, Cl, NMe_2, OMe, morpholino and COOEt; and
R^4 is methyl.

13. Use according to claim 12 wherein:
R^2 is H or NO_2; and
R^3 is Cl or F.

14. Use according to claim 1 wherein said compound is of formula Ib



Ib

wherein one of X and Y is S, and the other is NH or N-R^5; and
R^{2-5} are as defined in claim 1.

15. Use according to claim 14 wherein:
R^2 is selected from H, OH, NO_2 and alkyl;
R^3 is selected from H, halogen, alkoxy, alkyl, N-$(alkyl)_2$ and OH; and
R^4 and R^5 are each independently alkyl.

16. Use according to claim 15 wherein:
R^2 is selected from H, OH, NO_2 and Me;
R^3 is selected from H, Cl, F, OMe, Me, NMe_2 and OH; and
R^4 and R^5 are both Me.

17. Use according to any one of claims 1 to 16 wherein said compound of formula I is selected from the following:

3,5-Dimethyl-4-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[1]**;
4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[2]**;
4-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[3]**;
3,5-Dimethyl-4-[2-(4-trifluoromethyl-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[4]**;
4-[2-(4-Iodo-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[5]**;
4-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[6]**;
3,5-Dimethyl-4-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[7]**;
4-[2-(3-Iodo-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[8]**;
4-[2-(4-Chloro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[9]**;
4-[2-(3-Hydroxy-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[10]**;
4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[11]**;
4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[12]**;
4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide **[13]**;
[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[14]**;
N-[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-N',N'-dimethyl-benzene-1,4-diamine **[15]**;
[4-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[16]**;
[4-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine **[17]**;
[4-(5-Chloro-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[18]**;

[4-(5-Dimethylaminomethyl-2,4-dimethyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-(4-fluoro-phenyl)-amine **[19]**;

4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[20]**;

N^4-[4-(2,4-Dimethyl-5-nitro-1H-pyrrol-3-yl)-pyrimidin-2-yl]-N^1,N^1-dimethyl-2-nitro-benzene-1,4-diamine **[21]**;

4-[2-(3-Fluoro-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[22]**;

5-[2-(4-Chloro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[23]**;

5-[2-(4-Methoxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[24]**;

5-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[25]**;

5-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[26]**;

(4-Fluoro-phenyl)-[4-(2-methyl-4-phenyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-amine **[27]**

5-[2-(4-Fluoro-3-nitro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[28]**;

2-Chloro-4-[4-(4-methyl-2-methylamino-thiazol-5-yl)-pyrimidin-2-ylamino]-benzoic acid ethyl ester **[29]**;

[4-(2-Amino-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine **[30]**;

3,4-Dimethyl-5-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[32]**;

5-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[33]**;

5-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[34]**;

[4-(2-Chloro-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-(3-nitro-phenyl)-amine **[35]**;

3,4-Dimethyl-5-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[36]**;

(4-Fluoro-3-methyl-phenyl)-[4-(2-methoxy-4-methyl-thiazol-5-yl)-pyrimidin-2-yl]-amine **[37]**;

4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[38]**; and

4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[39]**.

18. Use according to claim 17 wherein said compound is selected from the following:
3,5-Dimethyl-4-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[1]**;
4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[2]**;
4-[2-(3-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[6]**;
3,5-Dimethyl-4-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[7]**;
4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[11]**;
4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **[12]**;
4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide **[13]**;
4-[2-(3-Fluoro-4-methyl-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile **[22]**;
(4-Fluoro-phenyl)-[4-(2-methyl-4-phenyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-amine **[27]**;
3,4-Dimethyl-5-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[32]**;
5-[2-(4-Hydroxy-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[34]**;
3,4-Dimethyl-5-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[36]**;
5-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[37]**;
4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[38]**; and
4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[39]**.

19. Use according to claim 17 wherein said compound is selected from the following:
3,5-Dimethyl-4-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-1H-pyrrole-2-carbonitrile **[7]**;
4-[2-(4-Fluoro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carboxylic acid amide **[13]**;
(4-Fluoro-phenyl)-[4-(2-methyl-4-phenyl-1H-pyrrol-3-yl)-pyrimidin-2-yl]-amine **[27]**;
3,4-Dimethyl-5-[2-(3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[32]**;
3,4-Dimethyl-5-[2-(4-methyl-3-nitro-phenylamino)-pyrimidin-4-yl]-3H-thiazol-2-one **[36]**;
5-[2-(4-Fluoro-3-methyl-phenylamino)-pyrimidin-4-yl]-3,4-dimethyl-3H-thiazol-2-one **[37]**;
4-[2-(4-Dimethylamino-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[38]**; and
4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-1,3,5-trimethyl-1H-pyrrole-2-carbonitrile **[39]**.

20. Use according to any preceding claim wherein the diabetes is Type II diabetes.

21. Use of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 19 in the preparation of a medicament for treating a CNS disorder.

22. Use according to claim 21 wherein the CNS disorder is Alzheimer's disease.

23. Use according to claim 21 wherein the CNS disorder is a bipolar disorder.

24. Use of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 19 in the preparation of a medicament for treating a cardiovascular disorder.

25. Use according to claim 24 wherein the cardiovascular disorder is myocardial infarction.

26. Use of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 19 in the preparation of a medicament for treating a stroke.

27. Use of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 19 in the preparation of a medicament for treating alopecia.

28. Use according to any preceding claim wherein said compound of formula I, or pharmaceutically acceptable salt thereof, is admixed with a pharmaceutically acceptable diluent, excipient or carrier.

29. Use according to any preceding claim wherein said compound of formula I is administered in combination with one or more other active agents.

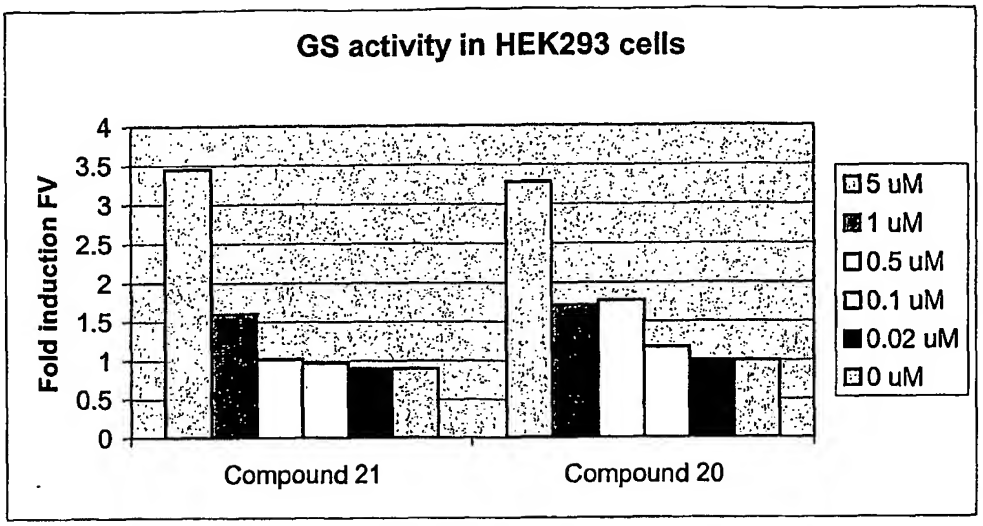
30. A method of treating a GSK3-dependent disorder, said method comprising administering to a subject in need thereof, a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 19 in an amount sufficient to inhibit GSK3.

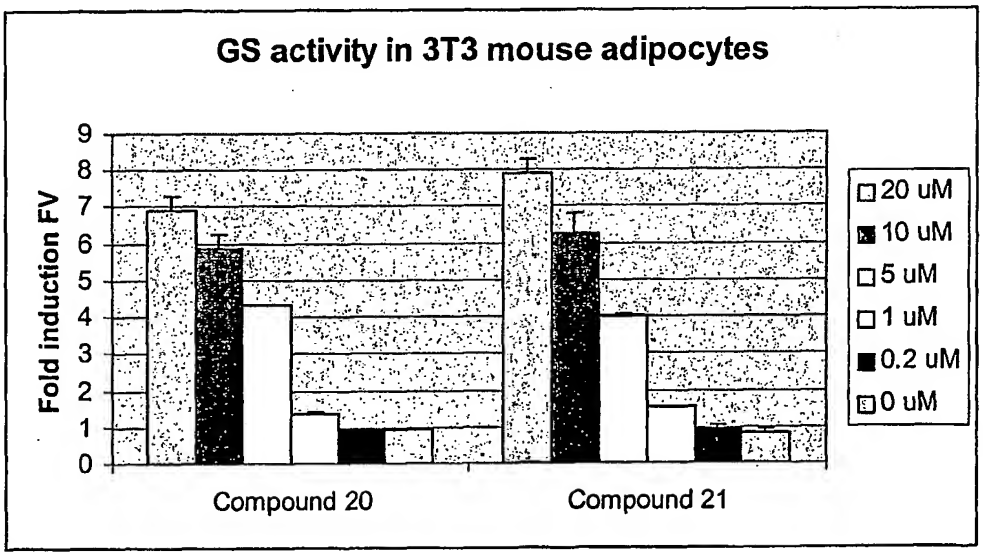
31. A method according to claim 30 wherein the compound of formula I, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to inhibit GSK3β.

32. A method according to claim 30 or 31 wherein the GSK3-dependent disorder is selected from diabetes, a CNS disorder, a cardiac disorder, stroke and alopecia.

33. A method of inhibiting GSK3 in a cell comprising contacting said cell with an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, such that GSK3 is inhibited in said cell.

34. A method of treating diabetes comprising inhibiting GSK3 by administering to a subject in need thereof, a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, such that treatment of diabetes occurs.


GS activity in HEK293 cells
Fold induction FV
4
3.5
3
2.5
2
1.5
1
0.5
0
Compound 21
Compound 20
5 uM
1 uM
0.5 uM
0.1 uM
0.02 uM
0 uM


GS activity in 3T3 mouse adipocytes
Fold induction FV
9
8
7
6
5
4
3
2
1
0
Compound 20
Compound 21
20 uM
10 uM
5 uM
1 uM
0.2 uM
0 uM

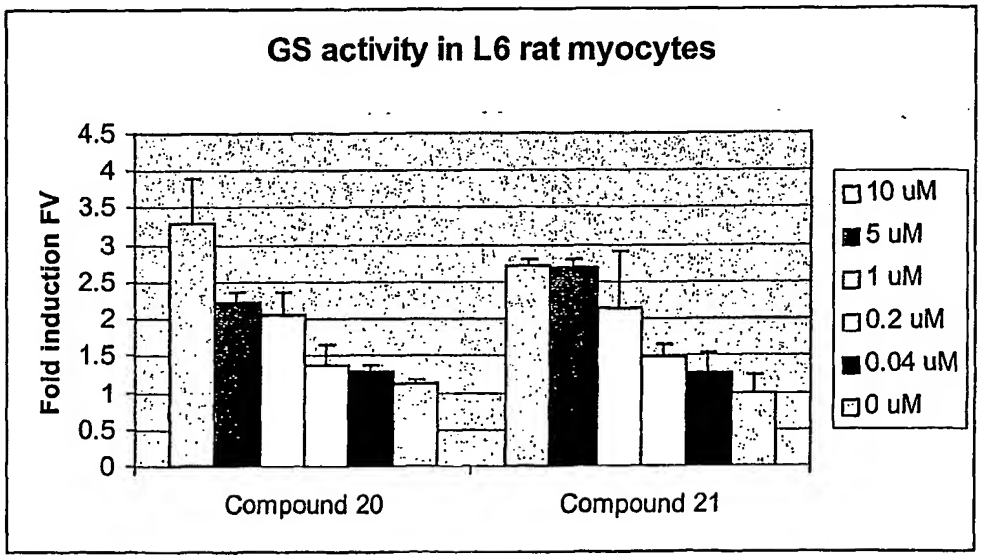
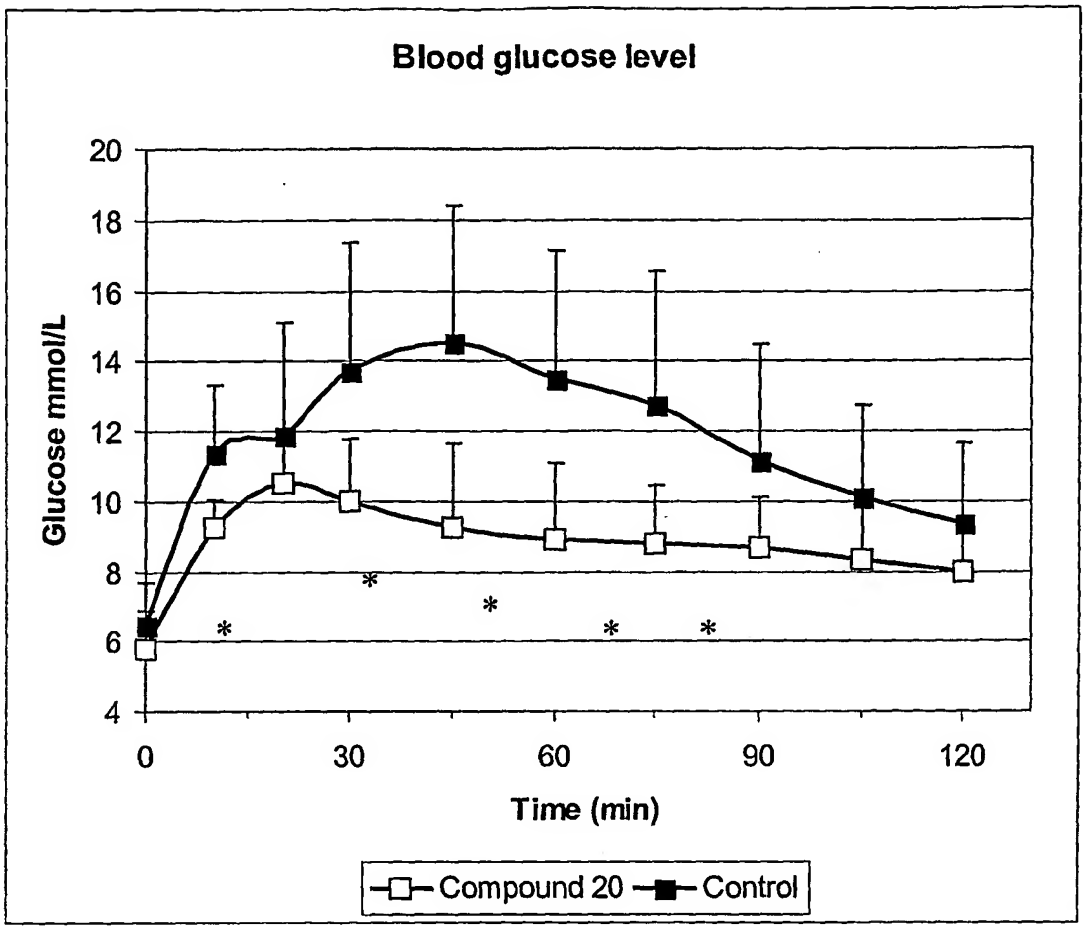

GS activity in L6 rat myocytes
Fold induction FV
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Compound 20
Compound 21
10 uM
5 uM
1 uM
0.2 uM
0.04 uM
0 uM

FIGURE 1



*: $p < 0.05$

FIGURE 2

INTERNATIONAL SEARCH REPORT

PCT/GB 03/05558

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/506 A61P5/48 A61P9/00 A61P17/14 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/029248 A (CYCLACEL LTD ;OSNOWSKI ANDREW (GB); WANG SHUDONG (GB); WOOD GAVIN) 10 April 2003 (2003-04-10) table 2 compound nr. 30 ---	24,27-33
X	US 2002/019404 A1 (FISCHER PETER M ET AL) 14 February 2002 (2002-02-14) claims 1,12 page 13, right-hand column, paragraph 2 formula 74 --- -/--	24,27-33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 2004	28/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Collura, A

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 233 461 A (AMERICAN CYANAMID CO) 26 August 1987 (1987-08-26) claims 1,18 table 1, page 13, first compound table 2, page 26, 3rd compound table 2, page 27, first and second compound	1-3,6, 17-19, 28-34
Y	WO 02/096905 A (HARRINGTON EDMUND ;VERTEX PHARMA (US); WANG JIAN (US); COCHRAN JOH) 5 December 2002 (2002-12-05) claims page 40, line 20-29	1-34
Y	US 6 417 185 B1 (GOFF DANE A ET AL) 9 July 2002 (2002-07-09) the whole document	1-34
Y	US 5 958 935 A (CELLTECH THERAPEUTICS LIMITED) 28 September 1999 (1999-09-28) examples 8,14,26	1-34
A	WO 02/066480 A (BERG STEFAN ;HELLBERG SVEN (SE); ASTRAZENECA AB (SE); BHAT RATAN ()) 29 August 2002 (2002-08-29) examples 14,15,38,96	1-34

INTERNATIONAL SEARCH REPORT

PCT/GB 03/05558

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 30-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/GB 03/05558

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03029248 A	10-04-2003	WO 03029248 A1	10-04-2003
US 2002019404 A1	14-02-2002	AU 4262901 A	08-10-2001
		CA 2401748 A1	04-10-2001
		CN 1420884 T	28-05-2003
		EP 1274705 A1	15-01-2003
		WO 0172745 A1	04-10-2001
		GB 2361236 A ,B	17-10-2001
		HU 0300382 A2	28-06-2003
		JP 2003528872 T	30-09-2003
		US 2003149057 A1	07-08-2003
EP 0233461 A	26-08-1987	AT 135699 T	15-04-1996
		AU 621461 B2	12-03-1992
		AU 5057890 A	26-07-1990
		AU 591223 B2	30-11-1989
		AU 6751887 A	16-07-1987
		BR 1100989 A3	09-11-1999
		CA 1320201 C	13-07-1993
		DE 3751742 D1	25-04-1996
		DE 3751742 T2	21-11-1996
		DK 15187 A	14-07-1987
		EP 0233461 A2	26-08-1987
		ES 2087056 T3	16-07-1996
		FI 870113 A ,B,	14-07-1987
		GR 3019455 T3	30-06-1996
		HU 43582 A2	30-11-1987
		IE 74202 B1	16-07-1997
		JP 2043824 C	09-04-1996
		JP 7080857 B	30-08-1995
		JP 62223177 A	01-10-1987
		KR 9004693 B1	02-07-1990
		NZ 218924 A	26-04-1990
		PH 25056 A	28-01-1991
		SG 47583 A1	17-04-1998
		US 4876252 A	24-10-1989
		US 4788195 A	29-11-1988
		ZA 8700219 A	26-08-1987
WO 02096905 A	05-12-2002	CA 2446756 A1	05-12-2002
		CA 2448319 A1	05-12-2002
		CN 1463270 T	24-12-2003
		EP 1392684 A1	03-03-2004
		NZ 529788 A	19-12-2003
		WO 02096905 A1	05-12-2002
		WO 02096910 A1	05-12-2002
		US 2003119856 A1	26-06-2003
		US 2003050331 A1	13-03-2003
		US 2003073852 A1	17-04-2003
		US 2003064984 A1	03-04-2003
US 6417185 B1	09-07-2002	US 2002156087 A1	24-10-2002
		AU 4956699 A	05-01-2000
		CN 1312807 T	12-09-2001
		EP 1087963 A1	04-04-2001
		JP 2003527303 T	16-09-2003
		WO 9965897 A1	23-12-1999
		US 2003130289 A1	10-07-2003

INTERNATIONAL SEARCH REPORT

PCT/GB 03/05558

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6417185 B1		US 6489344 B1	03-12-2002
US 5958935 A	28-09-1999	AU 7631496 A	11-06-1997
		DE 69627179 D1	08-05-2003
		DE 69627179 T2	29-01-2004
		EP 0862560 A1	09-09-1998
		ES 2195020 T3	01-12-2003
		WO 9719065 A1	29-05-1997
		US 6235746 B1	22-05-2001
WO 02066480 A	29-08-2002	BR 0207096 A	20-01-2004
		CA 2435177 A1	29-08-2002
		NO 20033677 A	02-10-2003
		WO 02066480 A2	29-08-2002